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☐	L54	L53 and (lutetium)adj(texaphyrin)	0
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☐	L52	L50 and benzoporphyrin	0
☐	L51	L50 and (lutetium)adj(texaphyrin)	0
☐	L50	424/145.1.ccls.	358
☐	L49	K47 and benzoporphyrin	0
☐	L48	L47 and (lutetium)adj(texaphyrin)	1
☐	L47	(514/912).ccls.	913
☐	L46	L44 and benzoporphyrin	0
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☐	L44	(514/453 |514/454).ccls.	570
☐	L43	(514/453).ccls.	303
☐	L42	L40 and (VEGF)adj(antibod?)	0
☐	L41	L40 and angiostatin	0
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☐	L39	(514/410).ccls.	510
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☐	L34	L33 and angiostatin	0
☐	L33	L28 and (lutetium)adj(texaphyrin)	5
		DB=PGPB,USPT,USOC,EPAB,JPAB,DWPI,TDBD; PLUR=YES; OP=OR	
☐	L32	L31 and (angiostatin)	2
☐	L31	L28 and (benzoporphyrin)	51
☐	L30	L28 and (benxoporphyrin)	0
☐	L29	L28 and (letetium)adj(texaphyrin)	0
☐	L28	(424/9.61 |424/155.1 |424/178.1).ccls.	2078
☐	L27	(Renno)adj(reem)adj(z)	3
☐	L26	(gragoudas)adj(evangelos)adj(s)	16

☐	L25	(miller)adj(joan)adj(w)	20
☐	L24	(method)same(closure)same(choroidal)adj(neovasculature)	1
☐	L23	(method)same(enhance)adj(closure)same(choroidal)adj(neovasculature)	0
☐	L22	(benzoporphyrin)same(anti-VEGF)	1
☐	L21	(benzoporphyrin)adj(derivative)same(anti-VEGF)	0
☐	L20	L19 and eye	13
☐	L19	L18 and photodynamic	13
☐	L18	L17 and enhancing	13
☐	L17	L16 and choroidal	13
☐	L16	(anti-VEGF)same(texaphyrin)	15
☐	L15	(ant-VEGF)same(texaphyrin)	0
	DB=PGPB; PLUR=YES; OP=OR		
☐	L14	US-20050261170-A1.did.	1
	DB=PGPB,USPT,USOC,EPAB,JPAB,DWPI,TDBD; PLUR=YES; OP=OR		
☐	L13	(benzoporphyrin)same(angiostatin)	1
☐	L12	(benzoporphyrin)adj(derivative)same(angiostatin)	0
☐	L11	(angiostatin)same(texaphyrin)	19
☐	L10	L8 and (choroidal)adj(vasculature)	6
☐	L9	L8 and (choroidal)adj(vascularture)	0
☐	L8	L1 and angiostatin	126
☐	L7	L6 and potentiation	30
☐	L6	L3 and (unwanted)adj(chroidal)ajd(neovasculature)	1412
☐	L5	L3 and (enhancing)adj(closure)	0
☐	L4	L3 and anti-VEGF	39
☐	L3	L2 and angiostatin	125
☐	L2	L1 and combination	2468
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L2 36 L1 AND ANGIOSTATIN

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L3 27 DUP REMOVE L2 (9 DUPLICATES REMOVED)

=> s l3 and combination
L4 5 L3 AND COMBINATION

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L5 5 DUP REMOVE L4 (0 DUPLICATES REMOVED)

=> d l5 1-5 cbib abs

L5 ANSWER 1 OF 5 EMBASE COPYRIGHT (c) 2006 Elsevier B.V. All rights reserved on STN
2005280378 EMBASE Adeno-associated virus-vectored gene therapy for retinal disease. Dinculescu A.; Glushakova L.; Min S.-H.; Hauswirth W.W.. Dr. W.W. Hauswirth, University of Florida College of Medicine, Department of Ophthalmology, J. Hillis Miller Health Center, Gainesville, FL 32610-0284, United States. hauswrth@eye1.eye.ufl.edu. Human Gene Therapy Vol. 16, No. 6, pp. 649-663 2005.
Refs: 173.
ISSN: 1043-0342. CODEN: HGTHE3
Pub. Country: United States. Language: English. Summary Language: English.
ED Entered STN: 20050721
AB Recombinant adeno-associated viral (AAV) vectors have become powerful gene delivery tools for the treatment of retinal degeneration in a variety of animal models that mimic corresponding human diseases. AAV vectors possess a number of features that render them ideally suited for retinal gene therapy, including a lack of pathogenicity, minimal immunogenicity,

and the ability to transduce postmitotic cells in a stable and efficient manner. In the sheltered environment of the retina, AAV vectors are able to maintain high levels of transgene expression in the retinal pigmented epithelium (RPE), photoreceptors, or ganglion cells for long periods of time after a single treatment. Each cell type can be specifically targeted by choosing the appropriate **combination** of AAV serotype, promoter, and intraocular injection site. The focus of this review is on examples of AAV-mediated gene therapy in those animal models of inherited retinal degeneration caused by mutations directly affecting the interacting unit formed by photoreceptors and the RPE. In each case discussed, expression of the therapeutic gene resulted in significant recovery of retinal structure and/or visual function. Because of the key role of the vasculature in maintaining a healthy retina, a summary of AAV gene therapy applications in animal models of retinal neovascular diseases is also included. .COPYRGT. Mary Ann Liebert, Inc.

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2005111257 EMBASE Antineovascular therapy, a novel antiangiogenic approach.
Shimizu K.; Asai T.; Oku N.. Dr. N. Oku, University of Shizouka, Department of Medical Biochemistry, School of Pharmaceutical Sciences, Shizouka, Japan. oku@u-shizouka-ken.ac.jp. Expert Opinion on Therapeutic Targets Vol. 9, No. 1, pp. 63-76 2005.
Refs: 105.
ISSN: 1472-8222. CODEN: EOTTAO
Pub. Country: United Kingdom. Language: English. Summary Language: English.

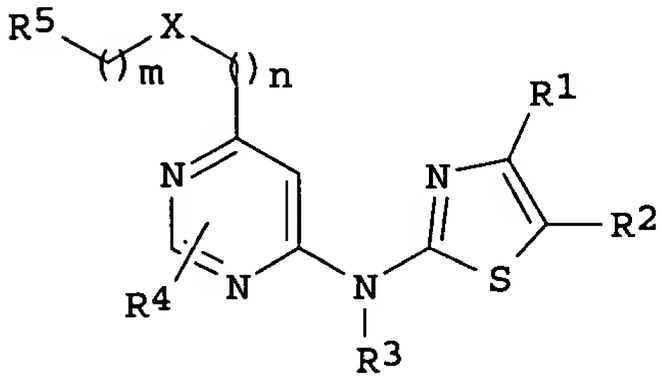
ED Entered STN: 20050324

AB Angiogenesis is a crucial event in tumour growth, since the growth of tumour cells depends on the supply of essentials such as oxygen and nutrients. Therefore, suppression of angiogenesis is expected to show potent therapeutic effects on various cancers. Additionally, this 'antiangiogenic therapy' is thought not only to eradicate primary tumour cells, but also suppress tumour metastases through disruption of haematogenous metastatic pathways. Tumour dormancy therapy does not aim to disrupt newly formed angiogenic vessels but aims to inhibit further formation of neovessels through inhibiting certain processes of angiogenesis. This raises a question of whether or not these antiangiogenic agents bring complete cure of tumours as complete cut-off of oxygen and nutrients is not expected by the treatment with these agents. This paper will review a novel antiangiogenic therapy, antineovascular therapy (ANET). ANET is categorised in antiangiogenic therapy but is different from tumour dormancy therapy using conventional angiogenic inhibitors: ANET aims to disrupt neovessels rather than to inhibit neovessel formation. ANET is based on the fact that angiogenic endothelial cells are growing cells and would be effectively damaged by cytotoxic agents when the agents are effectively delivered to the neovessels. The complete eradication of angiogenic endothelial cells may cause complete cut-off of essential supplies to the tumour cells and lead to indirect but strong cytotoxicity instead of cytostasis caused by the inhibition of angiogenesis. For the purpose of ANET, an angiogenic vasculature-targeting probe has been developed, by which cytotoxic anticancer agents are actively delivered to the angiogenic endothelial cells by using drug delivery system (DDS) technology. Another way to damage newly formed vessels by cytotoxic agents is achieved by metronomic-dosing chemotherapy. This chemotherapy shifts the target of chemotherapeutic agents from tumour cells to angiogenic endothelial cells by selective dosing schedule. Similarly, the shift of target from tumour cells to angiogenic endothelial cells enhanced therapeutic efficacy of cancer photo-dynamic therapy (PDT): in this antiangiogenic PDT, photosensitizers are delivered more to neovessel endothelial cells than to tumour cells. These therapeutic strategies would be clinically applied in the future. .COPYRGT. 2005 Ashley Publications Ltd.

L5 ANSWER 3 OF 5 CAPLUS COPYRIGHT 2006 ACS on STN

2004:412750 Document No. 140:423687 Preparation of thiazolylamino-substituted pyrimidines as kinase inhibitors. Hartman, George D.; Hoffman, Jacob M.; Smith, Anthony M.; Tucker, Thomas J. (Merck & Co., Inc., USA). PCT Int. Appl. WO 2004041164 A2 20040521, 102 pp. DESIGNATED STATES: W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG, TR. (English). CODEN: PIXXD2. APPLICATION: WO 2003-US34100 20031024. PRIORITY: US 2002-2002/PV422313 20021030.

GI



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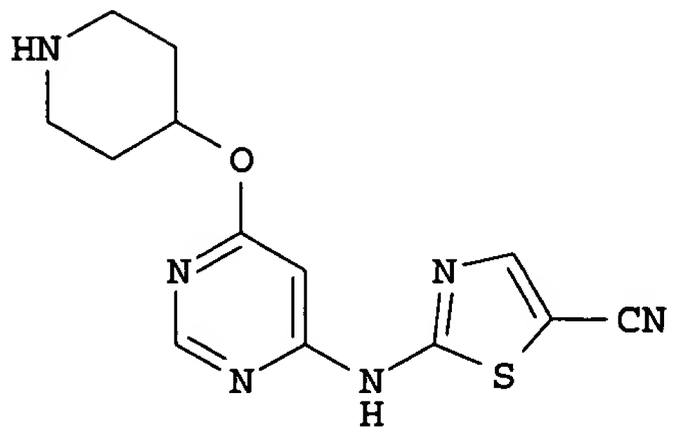

II

AB Title compds. I [X = O, S, amino; m,n = 0-3; R1-2, R4 = H, OH, alkoxy, CN, etc.; R3 = H, sulfonyl, acyl, carboxy, etc.; R5 = heterocyclyl] are prepared For instance, tert-Bu 4-[(6-aminopyrimidin-4-yl)oxy]piperidine-1-carboxylate (preparation given) is reacted with 2-chlorothiazole-5-carbonitrile (THF, NaH) and the resulting product deprotected (CH2Cl2, TFA) to give II. I inhibit, regulate and/or modulate kinase signal transduction; they are useful in the treatment of kinase-dependent diseases and conditions, such as angiogenesis, cancer, tumor growth, atherosclerosis, age related macular degeneration, retinal ischemia, macular edema, diabetic retinopathy and inflammatory diseases.

L5 ANSWER 4 OF 5 EMBASE

2003249645 EMBASE **Photodynamic therapy** for choroidal neovascularization. The Jules Gonin Lecture, Montreux, Switzerland, 1 September 2002. Miller J.W.. J.W. Miller, Angiogenesis and Laser Laboratories, Harvard Medical School, Massachusetts Eye and Ear Infirmary, Boston, MA, United States. jwmiller@meei.harvard.edu. Graefe's Archive for Clinical and Experimental Ophthalmology Vol. 241, No. 4, pp. 258-262 1 Apr 2003.

Refs: 30.
ISSN: 0721-832X. CODEN: GACODL
Pub. Country: Germany. Language: English.
ED Entered STN: 20030710
AB In summary, the targeted verteporfin and verteporfin-PVA were both more efficient at CNV closure than unbound verteporfin. VEGFR2-targeted verteporfin appeared to be selective when normal retina and choroid were treated, resulting in choriocapillaris closure with minimal effect on RPE or neurosensory retina. In contrast, the verteporfin-PVA control showed non-selective retinal damage. These positive findings will be pursued further in experimental models and will hopefully warrant clinical investigation in the future. Another direction that we also wish to pursue would be to modulate the PDT response in normal and diseased tissue using factors in the apoptosis pathway, and preliminary in vitro work supports this strategy [27]. We would also like to improve drug delivery for anti-angiogenic and neuroprotective agents and towards this end have been working on a trans-scleral drug delivery approach.

L5 ANSWER 5 OF 5 MEDLINE on STN
2001025053. PubMed ID: 11053300. **Photodynamic therapy** using Lu-Tex induces apoptosis in vitro, and its effect is potentiated by **angiostatin** in retinal capillary endothelial cells. Renno R Z; Delori F C; Holzer R A; Gragoudas E S; Miller J W. (Laser Laboratory, Retina Service, Massachusetts Eye and Ear Infirmary. Schepens Eye Research Institute, Harvard Medical School, Boston, USA.) Investigative ophthalmology & visual science, (2000 Nov) Vol. 41, No. 12, pp. 3963-71. Journal code: 7703701. ISSN: 0146-0404. Pub. country: United States. Language: English.
AB PURPOSE: To examine the effect of combining **angiostatin** with **photodynamic therapy** (PDT) using Lutetium Texaphyrin (Lu-Tex; Alcon, Fort Worth, TX) as a photosensitizer in bovine retinal capillary endothelial (BRCE) and retinal pigment epithelial (RPE) cells and to determine the mode of PDT-induced cell death in these cell lines. METHODS: Cultured BRCE and RPE cells were incubated with **angiostatin** (500 ng/ml) for 18 hours and subjected to Lu-Tex/PDT, using treatment parameters previously optimized (3 microgram/ml Lu-Tex for 30 minutes followed by timed irradiation at 732 nm). Cellular survival was assessed after a 1-week cellular proliferation. Data were analyzed using Student's t-test. Caspase 3 activity was monitored in cells after PDT using a fluorogenic substrate, (Asp-Glu-Val-Asp)-AFC (7-amino-4-trifluoromethyl coumarin) [DEVD-AFC], of caspase 3. After PDT, expression of Bcl-2, Bcl-x(L), Bax, and Bak was also examined in cell lysates by Western blot analysis. RESULTS: A synergistic cytotoxic effect of **angiostatin** and Lu-Tex/PDT was observed in BRCE cells at all fluences used (5, 10, and 20 J/cm(2); P </= 0.05). These findings applied only if **angiostatin** was delivered before PDT. No such interactive killing effect was observed in RPE cells. Caspase 3 activity was elevated within 10 minutes of PDT in BRCE and RPE cells and was fluence dependent. Differential modulation of Bcl-2 family members was observed after PDT in BRCE and RPE cells. CONCLUSIONS: The **combination** of **angiostatin** and Lu-Tex/PDT potentiates the cytotoxic effect of Lu-Tex/PDT on BRCE but not on RPE cells. This may provide a strategy to increase the selectivity of PDT in damaging capillary endothelial cells with less damage to RPE cells. Lu-Tex/PDT induces rapid caspase-dependent apoptosis in BRCE and RPE cells. Furthermore, Lu-Tex/PDT induces apoptosis through selective modulation of members of the Bcl-2 family and differs between BRCE and RPE cells.

=> d l3 1-27 cbib abs

L3 ANSWER 1 OF 27 CAPLUS COPYRIGHT 2006 ACS on STN
2005:696640 Document No. 143:199740 Onconase complex conjugated with folate for diagnosis and treatment of cancer, infection, cardiovascular disorder and autoimmune disease. Hansen, Hans J.; McBride, William J.; Goldenberg,

David M.; Rossi, Edmund A.; Chang, Chien-Hsing Ken (Immunomedics, Inc., USA). PCT Int. Appl. WO 2005069994 A2 20050804, 40 pp. DESIGNATED STATES: W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IS, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG, TR. (English). CODEN: PIXXD2. APPLICATION: WO 2005-US2193 20050124. PRIORITY: US 2004-2004/PV538396 20040122.

AB Because the folate receptor (also called the folate binding protein, FBP) is overexpressed on certain malignant cell types, targeting of the folate receptor has been proposed as a potential mechanism for delivery of drugs and/or radiopharmaceuticals to treat cancer. Onconase and/or variants with ribonucleolytic activity, such as rapLR1, present useful therapeutic mols. for preparing folate conjugates and complexes. The conjugates and complexes can be targeted to and internalized by targeted tissues. The conjugates and complexes may be formulated with a pharmaceutically acceptable excipient to form a primary therapeutic agent. The conjugates and complexes may be useful as primary therapeutic agents, which may be administered with addnl. therapeutic or diagnostic agents. Also disclosed are kits that include the conjugates and complexes.

L3 ANSWER 2 OF 27 EMBASE

2005280378 EMBASE Adeno-associated virus-vectored gene therapy for retinal disease. Dinculescu A.; Glushakova L.; Min S.-H.; Hauswirth W.W.. Dr. W.W. Hauswirth, University of Florida College of Medicine, Department of Ophthalmology, J. Hillis Miller Health Center, Gainesville, FL 32610-0284, United States. hauswrth@eye1.eye.ufl.edu. Human Gene Therapy Vol. 16, No. 6, pp. 649-663 2005.
Refs: 173.
ISSN: 1043-0342. CODEN: HGTHE3
Pub. Country: United States. Language: English. Summary Language: English.

ED Entered STN: 20050721

AB Recombinant adeno-associated viral (AAV) vectors have become powerful gene delivery tools for the treatment of retinal degeneration in a variety of animal models that mimic corresponding human diseases. AAV vectors possess a number of features that render them ideally suited for retinal gene therapy, including a lack of pathogenicity, minimal immunogenicity, and the ability to transduce postmitotic cells in a stable and efficient manner. In the sheltered environment of the retina, AAV vectors are able to maintain high levels of transgene expression in the retinal pigmented epithelium (RPE), photoreceptors, or ganglion cells for long periods of time after a single treatment. Each cell type can be specifically targeted by choosing the appropriate combination of AAV serotype, promoter, and intraocular injection site. The focus of this review is on examples of AAV-mediated gene therapy in those animal models of inherited retinal degeneration caused by mutations directly affecting the interacting unit formed by photoreceptors and the RPE. In each case discussed, expression of the therapeutic gene resulted in significant recovery of retinal structure and/or visual function. Because of the key role of the vasculature in maintaining a healthy retina, a summary of AAV gene therapy applications in animal models of retinal neovascular diseases is also included. .COPYRGT. Mary Ann Liebert, Inc.

L3 ANSWER 3 OF 27 EMBASE

2005304057 EMBASE Targeting angiogenesis, the underlying disorder in neovascular age-related macular degeneration. Ng E.W.M.; Adamis A.P.. Dr. A.P. Adamis, Eyetech Pharmaceuticals, Inc., 3 Times Square, New York, NY 10036, United States. Tony.Adamis@eyetech.com. Canadian Journal of Ophthalmology Vol. 40, No. 3, pp. 352-368 2005.
Refs: 130.

ISSN: 0008-4182. CODEN: CAJOBA
Pub. Country: Canada. Language: English. Summary Language: English; French.
ED Entered STN: 20050728
AB Angiogenesis has a causal role in many diseases, including neovascular age-related macular degeneration (AMD). Identification of key regulators of angiogenesis, including vascular endothelial growth factor (VEGF), fibroblast growth factor 2, pigment epithelium-derived growth factor, angiopoietins and extracellular matrix molecules, has facilitated the development of novel therapeutic agents that target the underlying pathological angiogenic process. Among these, VEGF serves as a "master switch" for many ocular neovascular conditions through its promotion of endothelial cell proliferation and survival, vascular permeability and ocular inflammation. Two anti-VEGF agents are now clinically available: bevacizumab, an antibody for metastatic colorectal cancer, and pegaptanib sodium, an aptamer for neovascular AMD. Unlike bevacizumab, which binds all VEGF isoforms, pegaptanib targets only VEGF (165), the isoform responsible for pathological ocular neovascularization and thus an ideal target for treatment of AMD. Although other therapies targeting angiogenesis in AMD are in clinical development, to date, pegaptanib is the only therapy approved by the Food and Drug Administration of the United States for the treatment of all neovascular AMD and represents a valuable addition to the hitherto limited options available for patients.

L3 ANSWER 4 OF 27 EMBASE
2005111257 EMBASE Antineovascular therapy, a novel antiangiogenic approach.
Shimizu K.; Asai T.; Oku N.. Dr. N. Oku, University of Shizouka, Department of Medical Biochemistry, School of Pharmaceutical Sciences, Shizouka, Japan. oku@u-shizouka-ken.ac.jp. Expert Opinion on Therapeutic Targets Vol. 9, No. 1, pp. 63-76 2005.
Refs: 105.
ISSN: 1472-8222. CODEN: EOTTAO
Pub. Country: United Kingdom. Language: English. Summary Language: English.
ED Entered STN: 20050324
AB Angiogenesis is a crucial event in tumour growth, since the growth of tumour cells depends on the supply of essentials such as oxygen and nutrients. Therefore, suppression of angiogenesis is expected to show potent therapeutic effects on various cancers. Additionally, this 'antiangiogenic therapy' is thought not only to eradicate primary tumour cells, but also suppress tumour metastases through disruption of haematogenous metastatic pathways. Tumour dormancy therapy does not aim to disrupt newly formed angiogenic vessels but aims to inhibit further formation of neovessels through inhibiting certain processes of angiogenesis. This raises a question of whether or not these antiangiogenic agents bring complete cure of tumours as complete cut-off of oxygen and nutrients is not expected by the treatment with these agents. This paper will review a novel antiangiogenic therapy, antineovascular therapy (ANET). ANET is categorised in antiangiogenic therapy but is different from tumour dormancy therapy using conventional angiogenic inhibitors: ANET aims to disrupt neovessels rather than to inhibit neovessel formation. ANET is based on the fact that angiogenic endothelial cells are growing cells and would be effectively damaged by cytotoxic agents when the agents are effectively delivered to the neovessels. The complete eradication of angiogenic endothelial cells may cause complete cut-off of essential supplies to the tumour cells and lead to indirect but strong cytotoxicity instead of cytostasis caused by the inhibition of angiogenesis. For the purpose of ANET, an angiogenic vasculature-targeting probe has been developed, by which cytotoxic anticancer agents are actively delivered to the angiogenic endothelial cells by using drug delivery system (DDS) technology. Another way to damage newly formed vessels by cytotoxic agents is achieved by metronomic-dosing chemotherapy. This chemotherapy shifts the target of chemotherapeutic agents from tumour cells to angiogenic endothelial cells

by selective dosing schedule. Similarly, the shift of target from tumour cells to angiogenic endothelial cells enhanced therapeutic efficacy of cancer photo-dynamic therapy (PDT): in this antiangiogenic PDT, photosensitizers are delivered more to neovessel endothelial cells than to tumour cells. These therapeutic strategies would be clinically applied in the future. .COPYRGT. 2005 Ashley Publications Ltd.

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2005160028 EMBASE Pharmacological therapy in age-related macular degeneration (AMD). Zou Y.-H.; Chiou G.C.Y.. G.C.Y. Chiou, Dept. of Medical Pharmacol./Toxicol., College of Medicine, Texas A/M System Health Sci. Center, College Station, TX 77843, United States. gchiou@tamu.edu. International Journal of Ophthalmology Vol. 5, No. 1, pp. 8-18 2005. Refs: 73.
ISSN: 1672-5123. Pub. Country: China. Language: English. Summary Language: English; Chinese.

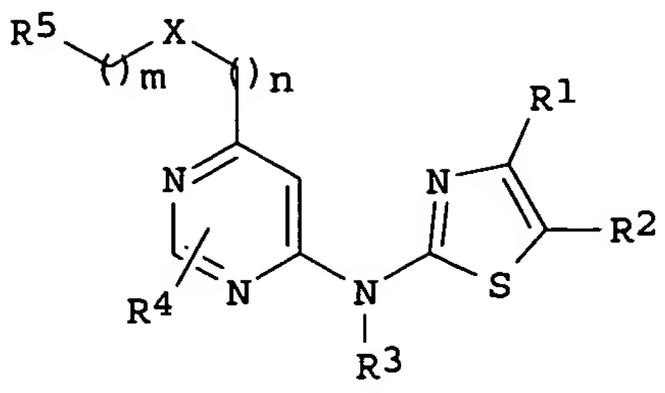
ED Entered STN: 20050428

AB • Age-related macular degeneration (AMD) is the leading cause of legal blindness in individuals aged over 65 in the United States and other industrialized nations. Till now, we have limited choices of treatment for this kind of disease. Treatment available can be grouped into two major categories: physical and pharmacological therapies. The former received extensive attention with little success whereas the latter attract new attention with great hope of success. The pharmacological therapies include **photodynamic therapy** (PDT), steroids, vascular endothelial growth factor (VEGF) inhibitors, extracellular matrix (ECM) modifiers, gene therapy, nutrition supplements, choroidal blood flow facilitators and the like. PDT treatment is the only available effective treatment for certain forms of neovascular AMD. Anecortave acetate, as a synthetic derivative of cortisol, might stabilize vision in patients with predominantly classic subfoveal choroidal neovascularization (CNV) for up to 6mo through subtenon juxtascleral depot application. Intravitreous injection of VEGF aptamer stabilized or improved vision in 87.5% of patients with subfoveal CNV 3mo after treatment. Malfunction of choroidal blood flow is found in early stage of AMD. Elevation of intravascular pressure is the crucial hemodynamic factor in age-related macular degeneration, resulting in a decrease of the blood flow of choriocapillaries. Chain reactions are triggered which lead to retinal pigment epithelium (RPE) degeneration, Bruch's membrane breakdown, CNV formation, AMD and blindness in the end. Therefore, specific drugs that can increase the choroidal blood flow could be very useful to prevent the AMD from developing and worsening. Although most of them are still in the experimental stage, it is hopeful to find a way to treat AMD at the early stage and to prevent the disease to be triggered and developed.

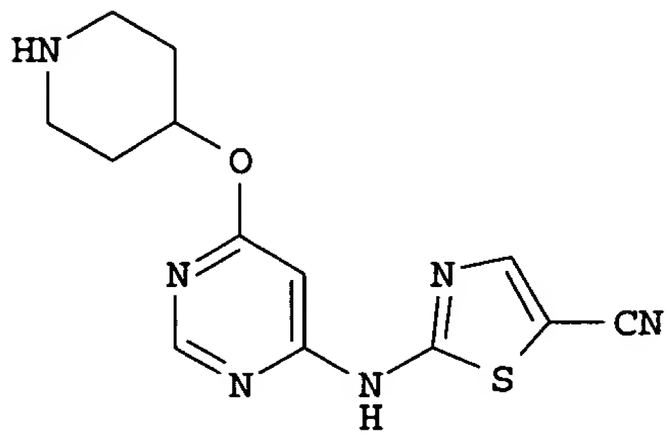
L3 ANSWER 6 OF 27 CAPLUS COPYRIGHT 2006 ACS on STN

2004:412750 Document No. 140:423687 Preparation of thiazolylamino-substituted pyrimidines as kinase inhibitors. Hartman, George D.; Hoffman, Jacob M.; Smith, Anthony M.; Tucker, Thomas J. (Merck & Co., Inc., USA). PCT Int. Appl. WO 2004041164 A2 20040521, 102 pp. DESIGNATED STATES: W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG, TR. (English). CODEN: PIXXD2. APPLICATION: WO 2003-US34100 20031024. PRIORITY: US 2002-2002/PV422313 20021030.

GI



I



II

AB Title compds. I [X = O, S, amino; m,n = 0-3; R1-2, R4 = H, OH, alkoxy, CN, etc.; R3 = H, sulfonyl, acyl, carboxy, etc.; R5 = heterocyclyl] are prepared For instance, tert-Bu 4-[(6-aminopyrimidin-4-yl)oxy]piperidine-1-carboxylate (preparation given) is reacted with 2-chlorothiazole-5-carbonitrile (THF, NaH) and the resulting product deprotected (CH2Cl2, TFA) to give II. I inhibit, regulate and/or modulate kinase signal transduction; they are useful in the treatment of kinase-dependent diseases and conditions, such as angiogenesis, cancer, tumor growth, atherosclerosis, age related macular degeneration, retinal ischemia, macular edema, diabetic retinopathy and inflammatory diseases.

L3 ANSWER 7 OF 27 CAPLUS COPYRIGHT 2006 ACS on STN

2004:934160 Document No. 141:388650 Anti-CD74 immunoconjugates and their therapeutic and diagnostic uses. Griffiths, Gary L.; Hansen, Hans J.; Goldenberg, David M.; Lundberg, Bo B. (Immunomedics, Inc., USA). U.S. Pat. Appl. Publ. US 2004219203 A1 20041104, 44 pp., Cont.-in-part of U.S. Ser. No. 377,122. (English). CODEN: USXXCO. APPLICATION: US 2003-706852 20031112. PRIORITY: US 2003-2003/377122 20030303; US 2003-2003/350096 20030124; US 2002-2002/314330 20021209; US 2001-2001/965796 20011001; US 2000-2000/590284 20000609; US 1999-307816 19990510; US 2003-2003/PV47883U 20030617; US 2002-2002/PV360259 20020301.

AB Disclosed are compns. that include anti-CD74 immunoconjugates and a therapeutic and/or diagnostic agent. Also disclosed are methods for preparing the immunoconjugates and using the immunoconjugates in diagnostic and therapeutic procedures. The compns. may be part of a kit for administering the anti-CD74 immunoconjugates compns. in therapeutic and/or diagnostic methods. Anti-CD74 binding mols. are conjugated to the one or more lipids by one or more of a sulfide linkage, a hydrazone linkage, a hydrazine linkage, an ester linkage, an amido linkage, an amino linkage, an imino linkage, a thiosemicarbazone linkage, a semicarbazone linkage, an oxime linkage, a carbon-carbon linkage. Anti-CD74 immunoconjugates comprise a drug, a prodrug, a toxin, an enzyme, a radioisotope, an immunomodulator, a cytokine, a hormone, an antibody., an oligonucleotide, or a photodynamic agent.

L3 ANSWER 8 OF 27 EMBASE COPYRIGHT (c) 2006 Elsevier B.V. All rights reserved on STN

2004306893 EMBASE Gene therapy for proliferative ocular diseases. McFarland T.J.; Zhang Y.; Appukuttan B.; Stout J.T.. J.T. Stout, Casey Eye Institute, OHSU, 3375 SW Terwilliger BLVD, Portland, OR 97239, United States. stoutt@ohsu.edu. Expert Opinion on Biological Therapy Vol. 4, No. 7, pp. 1053-1058 2004.
Refs: 77.
ISSN: 1471-2598. CODEN: EOBTA2
Pub. Country: United Kingdom. Language: English. Summary Language: English.
ED Entered STN: 20040819
AB Proliferative ocular diseases encompass a wide variety of pathological processes with adverse cellular differentiation, proliferation and migration as common features. Pathologies may involve neovascular responses associated with diabetic retinopathy, retinopathy of prematurity or age-related macular degeneration. These diseases are quite prevalent and account for substantial visual impairment and blindness worldwide. Although treatment strategies are largely surgical, advances in our understanding of the proteins crucial to cell transdifferentiation, proliferation and migration, along with better gene transfer techniques, have greatly increased the potential for biological treatment options. In this report, the most common proliferative ocular vascular diseases and existing therapeutic modalities will be reviewed and an overview of possible gene therapy options will be discussed, along with potential candidate genes.

L3 ANSWER 9 OF 27 EMBASE COPYRIGHT (c) 2006 Elsevier B.V. All rights reserved on STN
2005537734 EMBASE Cancer anti-angiogenic therapy. Shimizu K.; Oku N.. N. Oku, Department of Medical Biochemistry, University of Shizuoka, School of Pharmaceutical Sciences, Yada, Shizuoka 422-8526, Japan. oku@u-shizuoka-ken.ac.jp. Biological and Pharmaceutical Bulletin Vol. 27, No. 5, pp. 599-605 2004.
Refs: 113.
ISSN: 0918-6158. CODEN: BPBLEO
Pub. Country: Japan. Language: English. Summary Language: English.
ED Entered STN: 20051215
AB Tumor angiogenesis affords new targets for cancer therapy, since inhibition of angiogenesis suppresses tumor growth by cutting out the supply of oxygen and nutrients. Anti-angiogenic therapy is thought to be free of the severe side effects that are usually seen with cytotoxic anticancer drugs. Furthermore, anti-angiogenic therapy is thought not only to eradicate primary tumor tissues, but also to suppress tumor metastases. However, it is uncertain whether this therapy causes tumor regression because it inhibits only angiogenic events. Recently, a novel anti-angiogenic therapy called anti-neovascular therapy (ANET) has become notable. This therapy inflicts indirect lethal damage on tumor cells by damaging newly formed blood vessels using anti-cancer drugs targeting the angiogenic vasculature, since cytotoxic anti-cancer drugs cause damage to proliferating neovascular endothelial cells as well as tumor cells. Moreover, neovascular endothelial cells would not be expected to acquire drug-resistance. Traditional chemotherapy, which directly targets tumor cells, has potential problems such as low specificity and severe side effects. On the contrary, in ANET, severe side effects may be suppressed, since traditional anti-cancer agents are delivered to the neovessels by DDS technology. Besides the usage of DDS technology, anti-neovascular scheduling of chemotherapy, or metronomic-dosing chemotherapy, has also been attempted in which anti-cancer drugs are administered on a schedule to damage neovessels. In this review, we describe traditional anti-angiogenic therapy and ANET. We also discuss anti-angiogenic cancer **photodynamic therapy** (PDT), since PDT is clinically applied to treat age-related macular degeneration (AMD), in which uncontrolled angiogenesis occurs. .COPYRGT. 2004 Pharmaceutical Society of Japan.

L3 ANSWER 10 OF 27 SCISEARCH COPYRIGHT (c) 2006 The Thomson Corporation on

STN
2003:1054374 The Genuine Article (R) Number: 709CH. Enhanced **photodynamic therapy** using **angiostatin** with verteporfin PDT in a laser-injury rat model. Terada Y (Reprint); Michaud N A; Connolly E J; Lane A; Ohtsuki H; Gragoudas E S; Miller J W. Massachusetts Eye & Ear Infirm, Retina Serv, Angiogenesis & Laser Lab, Boston, MA 02114 USA; Okayama Univ, Sch Med, Okayama 700, Japan. INVESTIGATIVE OPHTHALMOLOGY & VISUAL SCIENCE (MAY 2003) Vol. 44, Supp. [1], pp. U408-U408. MA 1749. ISSN: 0146-0404. Publisher: ASSOC RESEARCH VISION OPHTHALMOLOGY INC, 12300 TWINBROOK PARKWAY, ROCKVILLE, MD 20852-1606 USA. Language: English.

L3 ANSWER 11 OF 27 EMBASE COPYRIGHT (c) 2006 Elsevier B.V. All rights reserved on STN
2003240955 EMBASE [Angiogenesis and lymphangiogenesis in the cornea. Pathogenesis, clinical implications and treatment options]. ANGIOGENESE UND LYMPHANGIOGENESE IN DER HORNHAUT. PATHOGENESE, KLINISCHE BEDEUTUNG UND THERAPIEOPTIONEN. Cursiefen C.; Seitz B.; Dana M.R.; Streilien J.W.. Dr. C. Cursiefen, Augenklinik mit Poliklinik, F.-Alexander-Univ. Erlangen-Nurnberg, Erlangen, Germany. cursiefen@vision.eri.harvard.edu. Ophthalmologe Vol. 100, No. 4, pp. 292-299 1 Apr 2003.
Refs: 30.
ISSN: 0941-293X. CODEN: OHTHEJ
Pub. Country: Germany. Language: German. Summary Language: English; German.
ED Entered STN: 20030710
AB Background. Whereas the normal cornea is devoid of blood and lymphatic vessels, both can invade the cornea secondary to a variety of corneal diseases and after surgery. This not only reduces visual acuity, but also renders such a cornea high-risk, if subsequent corneal transplantation is performed. Methods. A PUBMED-based literature search was carried out. Results. Current knowledge on pathogenesis, clinical implications and treatment modalities for corneal neovascularization is discussed. Conclusions. Novel anti-angiogenic and antilymphangiogenic therapeutic strategies should reduce blindness associated with corneal neovascularization and subsequent graft rejection.

L3 ANSWER 12 OF 27 EMBASE COPYRIGHT (c) 2006 Elsevier B.V. All rights reserved on STN
2003360035 EMBASE Retinopathy of prematurity: Molecular pathology and therapeutic strategies. Mechoulam H.; Pierce E.A.. Dr. E.A. Pierce, Scheie Eye Institute, University of Pennsylvania, 305 Stellar Chance Labs., 422 Curie Boulevard, Philadelphia, PA 19104, United States. epierce@mail.med.upenn.edu. American Journal of PharmacoGenomics Vol. 3, No. 4, pp. 261-277 2003.
Refs: 190.
ISSN: 1175-2203. CODEN: AJPMC8
Pub. Country: New Zealand. Language: English. Summary Language: English.
ED Entered STN: 20030925
AB Retinopathy of prematurity (ROP) is an ischemia-induced proliferative retinopathy, which affects premature infants with low birth weight. It is a leading cause of visual impairment and blindness in children, and shares pathophysiological characteristics with other common ocular diseases such as diabetic retinopathy, central vein occlusion, and age-related macular degeneration. Pathologically similar inherited diseases such as Norrie disease suggest a possible genetic component in the susceptibility to ROP. The process of retinal neovascularization in ROP and in animal models of oxygen-induced retinopathy is complex, and involves angiogenic factors, such as vascular endothelial growth factor, and basement membrane components. Potential medical therapies for ROP, including modulators of angiogenic factors, inhibitors of basement membrane changes, endogenous inhibitors such as pigment epithelium derived factor, and anti-inflammatory drugs, have shown efficacy against neovascularization in several animal models. Some of these therapies are in clinical trials now for diabetic retinopathy and age-related macular degeneration, and in the

future may prove efficacious for the treatment of ROP.

L3 ANSWER 13 OF 27 EMBASE COPYRIGHT (c) 2006 Elsevier B.V. All rights reserved on STN

2003249645 EMBASE **Photodynamic therapy** for choroidal neovascularization. The Jules Gonin Lecture, Montreux, Switzerland, 1 September 2002. Miller J.W.. J.W. Miller, Angiogenesis and Laser Laboratories, Harvard Medical School, Massachusetts Eye and Ear Infirmary, Boston, MA, United States. jwmiller@meei.harvard.edu. Graefe's Archive for Clinical and Experimental Ophthalmology Vol. 241, No. 4, pp. 258-262 1 Apr 2003.
Refs: 30.
ISSN: 0721-832X. CODEN: GACODL
Pub. Country: Germany. Language: English.

ED Entered STN: 20030710

AB In summary, the targeted verteporfin and verteporfin-PVA were both more efficient at CNV closure than unbound verteporfin. VEGFR2-targeted verteporfin appeared to be selective when normal retina and choroid were treated, resulting in choriocapillaris closure with minimal effect on RPE or neurosensory retina. In contrast, the verteporfin-PVA control showed non-selective retinal damage. These positive findings will be pursued further in experimental models and will hopefully warrant clinical investigation in the future. Another direction that we also wish to pursue would be to modulate the PDT response in normal and diseased tissue using factors in the apoptosis pathway, and preliminary in vitro work supports this strategy [27]. We would also like to improve drug delivery for anti-angiogenic and neuroprotective agents and towards this end have been working on a trans-scleral drug delivery approach.

L3 ANSWER 14 OF 27 BIOSIS COPYRIGHT (c) 2006 The Thomson Corporation on STN

2003:529243 Document No.: PREV200300524981. ENHANCED **PHOTODYNAMIC THERAPY** USING **ANGIOSTATIN** WITH VERTEPORFIN PDT IN A LASER - INJURY RAT MODEL. Terada, Y. [Reprint Author]; Michaud, N. A. [Reprint Author]; Connolly, E. J. [Reprint Author]; Lane, A. [Reprint Author]; Ohtsuki, H.; Gragoudas, E. S. [Reprint Author]; Miller, J. W. [Reprint Author]. Retina Service, Angiogenesis and Laser Laboratory, Mass Eye and Ear Infirmary, Boston, MA, USA. ARVO Annual Meeting Abstract Search and Program Planner, (2003) Vol. 2003, pp. Abstract No. 1749. cd-rom.
Meeting Info.: Annual Meeting of the Association for Research in Vision and Ophthalmology. Fort Lauderdale, FL, USA. May 04-08, 2003. Association for Research in Vision and Ophthalmology.
Language: English.

AB Purpose: Previous studies had shown increased cytotoxicity of verteporfin **photodynamic therapy** (PDT) combined with the anti-angiogenic drug **angiostatin** for bovine retinal microcapillary endothelium (bRME) but not for human retinal pigment epithelium (hRPE) in vitro. Here, we investigated the selectivity and the efficacy of PDT combined with **angiostatin** in vivo. Methods: Choroidal neovascular membranes (CNV) were induced in Brown-Norway rats using Argon/Dye laser. After the initial laser CNV induction, rats were treated with either **angiostatin** bolus injections intraperitoneally (12 and 24 hours before PDT) at 50 mg/kg or continuous administration of **angiostatin** through subcutaneously implanted osmotic pumps at 15mg/kg/day. Verteporfin PDT was performed at verteporfin dose of 3 or 6 mg/m2 using an irradiance of 600mW/cm2 and fluence of 10 and 25 J/cm2. Fluorescein angiograms performed 20 days after laser injury but before PDT, as well as 1 and 7 days after PDT were graded in a masked fashion using grading standards of CNV leakage. Non-parametric and parametric techniques were used to evaluate treatment effects. Results: **Angiostatin** alone did not prevent CNV growth using either model of administration. Bolus intraperitoneal administration of **angiostatin** prior to verteporfin PDT did not increase the efficacy of verteporfin PDT on CNV closure (P>.40 for

differences in leakage between eyes treated with PDT vs. PDT with **angiostatin** at both timepoints and fluences).Continuous subcutaneous administration of **angiostatin** was significantly associated with CNV closure (beta=2.63, P=.002) in regression analysis adjusting for the effects of fluence. Conclusions: Continuous administration of **angiostatin** potentiated the efficacy of verteporfin PDT for CNV closure in a laser-injury rat model. Combined therapy of anti-angiogenic drugs and PDT may limit the damage to normal structure and improve PDT results.

L3 ANSWER 15 OF 27 SCISEARCH COPYRIGHT (c) 2006 The Thomson Corporation on STN

2002:558926 The Genuine Article (R) Number: 567GZ. Adeno-associated virus type-2 expression of pigmented epithelium-derived factor or Kringles 1-3 of **angiostatin** reduce retinal neovascularization. Raisler B J; Berns K I; Grant M B; Beliaev D; Hauswirth W W (Reprint). Univ Florida, Dept Ophthalmol, Box 1002984, Gainesville, FL 32610 USA (Reprint); Univ Florida, Dept Ophthalmol, Gainesville, FL 32610 USA. PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF THE UNITED STATES OF AMERICA (25 JUN 2002) Vol. 99, No. 13, pp. 8909-8914. ISSN: 0027-8424. Publisher: NATL ACAD SCIENCES, 2101 CONSTITUTION AVE NW, WASHINGTON, DC 20418 USA. Language: English.

ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB Neovascular diseases of the retina include age-related macular degeneration and diabetic retinopathy, and together they comprise the leading causes of adult-onset blindness in developed countries. Current surgical, pharmaceutical, and laser therapies for age-related macular degeneration (AMD) rarely result in improved vision, do not significantly prevent neovascularization (NV), and often result in at least some vision loss. To address this therapeutic gap, we determined the efficacy of recombinant adeno-associated viral (rAAV) serotype-2-mediated expression of pigment epithelium-derived factor (PEDF) or Kringle domains 1-3 of **angiostatin** (K1K3) in reducing aberrant vessel formation in a mouse model of ischemia-induced retinal NV. Both PEDF and K1K3 are potent inhibitors of NV when injected directly, hence expression of these therapeutic factors from rAAV may provide long-term protection from neovascular eye disease. rAAV vectors expressing the therapeutic gene were injected into one eye of postnatal day 0 (P0) newborn mouse pups. Retinal NV was induced in P7 mice by exposure to elevated oxygen for 5 days followed by room air for another five days. Retinal NV was quantified by the number of vascular-endothelial-cell nuclei above the inner-limiting membrane in P17 eyes. The number of such vascular endothelial cell nuclei in eyes treated with rAAV-PEDF or rAAV-K1K3 was significantly reduced (both $P < 0.0000002$) compared with control eyes. Ocular protein levels detected by ELISA correlate well with the reduction in NV and confirm that expression of antineovascular agents from rAAV vectors may be a therapeutically useful treatment of retinal or choroidal neovascular disease.

L3 ANSWER 16 OF 27 SCISEARCH COPYRIGHT (c) 2006 The Thomson Corporation on STN

2002:679778 The Genuine Article (R) Number: 582JF. **Angiostatin** inhibits and regresses corneal neovascularization. Ambati B K; Joussen A M; Ambati J; Moromizato Y; Guha C; Javaherian K; Gillies S; O'Reilly M S; Adamis A P (Reprint). Harvard Univ, Massachusetts Eye & Ear Infirm, Dept Ophthalmol, 243 Charles St, Boston, MA 02114 USA (Reprint); Harvard Univ, Massachusetts Eye & Ear Infirm, Dept Ophthalmol, Boston, MA 02114 USA; Childrens Hosp, Surg Res Lab, Boston, MA 02115 USA; Harvard Univ, Sch Med, Boston, MA 02215 USA; Montefiore Med Ctr, Albert Einstein Coll Med, Dept Radiat Oncol, Bronx, NY 10467 USA; Lexigen Pharmaceut, Lexington, MA USA; Univ Texas, MD Anderson Canc Ctr, Div Radiat Oncol, Houston, TX 77030 USA. ARCHIVES OF OPHTHALMOLOGY (AUG 2002) Vol. 120, No. 8, pp. 1063-1068. ISSN: 0003-9950. Publisher: AMER MEDICAL ASSOC, 515 N STATE ST, CHICAGO, IL 60610 USA. Language: English.

ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB Objective: To determine the ability of **angiostatin** and the **angiostatin**-producing low-metastatic (LM) clone of Lewis lung carcinoma (LLC) to inhibit and regress corneal neovascularization, as compared with the nonangiostatin-producing high-metastatic (HM) clone.

Methods: Three groups of C57BL6/J mice underwent chemical and mechanical denudation of corneal and limbal epithelium. One group remained tumor free while the other 2 were implanted with LLC cells (either the HM or LM clones) subcutaneously the day before, 2 weeks after, or 4 weeks after denudation. Corneas were harvested 2 weeks after tumor implantation (at 2, 4, and 6 weeks after denudation for tumor-free mice). Neovascularization was quantified by CD31 immunostaining. In a second experiment, recombinant **angiostatin** was delivered continuously for 2 weeks via an osmotic pump in mice with established corneal neovascularization.

Results: The mean percentages of neovascularized corneal area in mice 2 weeks after LM-LLC implantation were 4.6%, 3.7%, and 37.0%, at 2, 4, and 6 weeks after scraping, respectively. In contrast, in the mice implanted with HM-LLC, the corresponding values were 45.4% (P =.01), 90.1% (P=.03), and 80.3% (P=.005). For tumor-free mice, the corresponding values were 62.0% (P=.003), 68.9% (P=.03), and 59.3% (P=.06). Mice implanted with **angiostatin** pumps had a 37.7% neovascularized corneal area 2 weeks after implantation and 4 weeks after scraping while mice implanted with sham pumps had 60.5% (P=.007).

Conclusion: **Angiostatin** inhibits and regresses corneal neovascularization induced by mechanical and alkali corneal injury.

Clinical Relevance: This appears to be the first evidence of biologically induced regression of corneal neovascularization, and the first direct demonstration of **angiostatin**-induced regression of neovascularization in any tissue.

L3 ANSWER 17 OF 27 EMBASE

2003006755 EMBASE [Age-related macular degeneration: A review of anti-angiogenic treatments]. TRAITEMENTS ANTI-ANGIOGENIQUES AU COURS DE LA DEGENERESCENCE MACULAIRE LIEE A L'AGE. Razavi S.; Coscas G.; Soubrane G.. G. Soubrane, Serv. Universitaire d'Ophtalmologie, Centre Hospitalier Intercommunal, 40 avenue de Verdun, 94010 Creteil, France. Journal Francais d'Ophtalmologie Vol. 25, No. 7, pp. 747-752 2002.
Refs: 42.
ISSN: 0181-5512. CODEN: JFOPDG
Pub. Country: France. Language: French. Summary Language: English; French.

ED Entered STN: 20030116

AB In Western countries, age-related macular degeneration is the leading cause of visual loss in people aged 65 and over. Laser photocoagulation has been shown to be beneficial in patients with extra- or juxta-foveal classic choroidal neovascularization (CNV), but the majority of patients with exudative maculopathy have occult or subfoveal CNV. Laser photocoagulation is plagued by recurrences, which occur in more than 50% of cases. Because of the limited efficacy of laser photocoagulation and the small number of patients who are eligible for treatment, investigators are attempting to develop new modalities to treat CNV. These modalities can be classified into three major categories: surgery, photodynamic and pharmacological treatments. The general mechanism, the regulation of ocular angiogenesis, and current anti-angiogenic treatments are the subject of this review of the recent literature.

L3 ANSWER 18 OF 27 MEDLINE on STN DUPLICATE 1

2002649629. PubMed ID: 12408983. Release of regulators of angiogenesis following Hypocrellin-A and -B **photodynamic therapy** of human brain tumor cells. Deininger Martin H; Weinschenk Toni; Morgalla Matthias H; Meyermann Richard; Schluesener Hermann J. (Institute of Brain Research, University of Tubingen, Calwer Strasse 3, D-72076 Tubingen, Germany.. martin.deininger@uni-tuebingen.de) . Biochemical and biophysical research communications, (2002 Nov 8) Vol. 298, No. 4, pp. 520-30. Ref: 83. Journal code: 0372516. ISSN: 0006-291X. Pub. country: United States.

Language: English.

AB **Photodynamic therapy** (PDT) is an innovative strategy for the treatment of solid neoplasms of the brain. Aside from inducing cell death in tumor cells, PDT induces endothelial cell death and promotes formation of blood clots; however, exact mechanisms that trigger these phenomena remain largely unknown. We now used Western blotting to analyze secretion of regulators of angiogenesis to the supernatants of one glioma, one macrophage, and one endothelial cell line following Hypocrellin-A and -B **photodynamic therapy.** We observed induction of proangiogenic VEGF (vascular endothelial growth factor) and of antiangiogenic sFlt-1, **angiostatin**, p43, allograft inflammatory factor-1, and connective tissue growth factor. Release of thrombospondin-1 was diminished in a glioma cell line supernatant. Endostatin release was induced in glioma cells and reduced in macrophages and endothelial cells. These data show that a wide range of antiangiogenic factors are secreted by brain tumor cells following Hypocrellin photochemotherapy. However, VEGF release is also induced thus suggesting both favorable and deleterious effects on tumor outgrowth.

L3 ANSWER 19 OF 27 SCISEARCH COPYRIGHT (c) 2006 The Thomson Corporation on STN

2003:955111 The Genuine Article (R) Number: 709CF. Modified verteporfin **photodynamic therapy** (PDT), PDT combined with **angiostatin** in vitro and in vivo. Terada Y (Reprint); Zacks D N; Connolly E J; Michaud N; Gragoudas E S; Miller J W. Harvard Univ, Sch Med, Massachusetts Eye & Ear Infirm, Retina Serv, Angiogenesis & Laser Res Lab, Boston, MA USA. INVESTIGATIVE OPHTHALMOLOGY & VISUAL SCIENCE (MAY 2002) Vol. 43, Supp. [1], pp. U114-U114. MA 574. ISSN: 0146-0404. Publisher: ASSOC RESEARCH VISION OPHTHALMOLOGY INC, 12300 TWINBROOK PARKWAY, ROCKVILLE, MD 20852-1606 USA. Language: English.

L3 ANSWER 20 OF 27 BIOSIS COPYRIGHT (c) 2006 The Thomson Corporation on STN

2003:143040 Document No.: PREV200300143040. Suppression of Preretinal Neovascularization by Recombinant Adeno-associated Virus Expressing **Angiostatin.** Lai, C.-C. [Reprint Author]; Wu, W.-C. [Reprint Author]; Chen, S.-L.; Xiao, X.; Tsai, T.-C.; Huan, S.-J.; Chen, T.-L. [Reprint Author]; Tsai, R.-F. [Reprint Author]; Tsao, Y.-P. [Reprint Author]. San Diego, CA, USA. ARVO Annual Meeting Abstract Search and Program Planner, (2002) Vol. 2002, pp. Abstract No. 1269. cd-rom. Meeting Info.: Annual Meeting of the Association For Research in Vision and Ophthalmology. Fort Lauderdale, Florida, USA. May 05-10, 2002. Language: English.

AB Purpose: To test the efficacy of recombinant adeno-associated virus (rAAV) vector expressing mouse **angiostatin** in suppressing experimental preretinal neovascularization in an albino rat model. Methods: rAAV-**angiostatin** and control virus rAAV-lacZ were delivered in vivo by intravitreous injection on Sprague-Dawley rats and the delivery was confirmed by reverse-transcriptase polymerase chain reaction (RT-PCR). For suppression of preretinal neovascularization, preretinal neovascularization was created by retinal vein occlusion 21 days after the injection. The retinal vein occlusion was induced by **photodynamic therapy** with systemic injection of rose bengal (40mg/kg) followed by an argon green laser. The animals were sacrificed 10 days after the retinal vein thrombosis and perfused with FITC-labelled dextran to serve as neovascularization analysis. After perfusion, those samples with evidence of neovascularization were quantified using an image analyzer. The retinas were also embedded in paraffin and serially sectioned at 6mum. The samples were stained with hematoxylin and eosin. Nuclei above the internal limiting membrane were then count in a masked manner. Results: The sizes of preretinal neovascularization in rAAV-**angiostatin** injected eyes were significantly smaller than the controlled eyes. Moreover, the number of vitreous cells was also less in experimental eyes. Conclusion: rAAV-**angiostatin** can successfully suppress the experimental preretinal neovascularization in albino rats. The results

showed the feasibility of gene therapy approach as treatment of preretinal neovascularization.

L3 ANSWER 21 OF 27 BIOSIS COPYRIGHT (c) 2006 The Thomson Corporation on STN

2003:142500 Document No.: PREV200300142500. Modified Verteporfin **Photodynamic Therapy** (PDT), PDT Combined With **Angiostatin** In Vitro and In Vivo. Terada, Y. [Reprint Author]; Zacks, D. N. [Reprint Author]; Connolly, E. J. [Reprint Author]; Michaud, N. [Reprint Author]; Gragoudas, E. S. [Reprint Author]; Miller, J. W. [Reprint Author]. Angiogenesis and Laser Research Laboratory, Retina Service, Mass Eye and Ear Infirmary, Harvard Medical School, Boston, MA, USA. ARVO Annual Meeting Abstract Search and Program Planner, (2002) Vol. 2002, pp. Abstract No. 574. cd-rom.
Meeting Info.: Annual Meeting of the Association For Research in Vision and Ophthalmology. Fort Lauderdale, Florida, USA. May 05-10, 2002.
Language: English.

AB Purpose: To investigate the selectivity and the efficacy of PDT combined with the anti-angiogenic drug **angiostatin** in vitro and in vivo. Methods: (in vitro) Human retinal pigment epithelial (hRPE) and bovine retinal microvascular endothelial cells (bRME) were maintained in conditioned media. Verteporfin PDT was performed on cells with or without prior exposure to 100ng/mL of **angiostatin.** Cellular survival was assessed at 24 hours after PDT. (in vivo) Choroidal neovascular membranes (CNV) were induced in Brown-Norway rats using Argon/Dye laser. Four groups were studied: 1. control rats (placebo), 2. **angiostatin** alone (50mg/kg) 1 and 2 weeks after CNV induction, 3. verteporfin PDT alone and 4. PDT plus 50mg/kg of **angiostatin** 12 and 24 hours prior to PDT at verteporfin dose of 3mg/m2 using an irradiance of 600mW/cm2 and fluence of 10 and 25 J/cm2. Fluorescein angiography was performed at 3 and 4 weeks after CNV induction and at 24 hours and 7 days after PDT, and graded in a masked standardized fashion. Results: In vitro results showed increased cytotoxicity for bRME but for hRPE when **angiostatin** was combined with verteporfn PDT. In vivo results showed that **angiostatin** alone did not prevent CNV, and there was no increased efficacy when **angiostatin** was administered prior to verteporfin PDT at the doses tested. Conclusion: **Angiostatin** potentiated the efficacy of verteporfin PDT for microvascular endothelium. However, in vivo **angiostatin** did not appear to potentiate the effect of verteporfin PDT on CNV at the doses tested.

L3 ANSWER 22 OF 27 CAPLUS COPYRIGHT 2006 ACS on STN

2001:597738 Document No. 135:149263 Methods and compositions for treating condition of the eye. Miller, Joan W.; Gragoudas, Evangelos S.; Renno, Reem Z. (Massachusetts Eye and Ear Infirmary, USA). PCT Int. Appl. WO 2001058240 A2 20010816, 46 pp. DESIGNATED STATES: W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, US, UG, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG, TR. (English). CODEN: PIXXD2. APPLICATION: WO 2001-US4231 20010209. PRIORITY: US 2000-PV181641 20000210.

AB Provided are methods and compns. for the **photodynamic therapy** (PDT) of ocular conditions characterized by the presence of unwanted choroidal neovasculature, for example, neovascular age-related macular degeneration. The selectivity and sensitivity of the PDT method can be enhanced by combining the PDT with an anti-angiogenesis factor, for example, **angiostatin** or endostatin, or with an apoptosis-modulating factor. Furthermore, the selectivity and sensitivity of the PDT may be further enhanced by coupling a targeting moiety to the photosensitizer so as to target the photosensitizer to choroidal

neovasculature.

L3 ANSWER 23 OF 27 SCISEARCH COPYRIGHT (c) 2006 The Thomson Corporation on STN

2001:724107 The Genuine Article (R) Number: 469FL. Suppression of choroidal neovascularization by adeno-associated virus vector expressing **angiostatin.** Lai C C; Wu W C; Chen S L; Xiao X; Tsai T C; Huan S J; Chen T L; Tsai R J F; Tsao Y P (Reprint). Chang Gung Mem Hosp, Dept Ophthalmol, 5 Fu-Hsin St, Tao Yuan 333, Taiwan (Reprint); Chang Gung Mem Hosp, Dept Ophthalmol, Tao Yuan 333, Taiwan; Natl Def Med Ctr, Dept Microbiol & Immunol, Taipei, Taiwan; Univ Pittsburgh, Dept Mol Genet & Biochem, Pittsburgh, PA 15260 USA; Vet Gen Hosp, Dept Med Res, Taipei 11217, Taiwan. INVESTIGATIVE OPHTHALMOLOGY & VISUAL SCIENCE (SEP 2001) Vol. 42, No. 10, pp. 2401-2407. ISSN: 0146-0404. Publisher: ASSOC RESEARCH VISION OPHTHALMOLOGY INC, 9650 ROCKVILLE PIKE, BETHESDA, MD 20814-3998 USA. Language: English.

ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB PURPOSE. To test the efficacy of a recombinant adeno-associated virus (rAAV) vector that expresses mouse **angiostatin** in suppressing experimental choroidal neovascularization (CN-V) in a rat model.

METHODS. An rAAV vector, rAAV-**angiostatin**, was constructed to deliver the mouse **angiostatin** gene. rAAV-**angiostatin** and a control virus, rAAV-lacZ, were delivered in vivo by subretinal injection in Brown Norway rats, and the delivery was confirmed by reverse-transcriptase polymerase chain reaction (RT-PCR). For a CNV suppression experiment, CNV was generated by fundus krypton laser photocoagulation 7 days after the viral vector injection and was evaluated by fluorescein angiography (FA) and histology. Apoptosis in retina was analyzed using the TUNEL assay. Inflammation in the retina was investigated by immunohistochemistry, using antibodies that recognize lymphocytes.

RESULTS. rAAV-**angiostatin** injection led to sustained expression of the **angiostatin** gene in chorioretinal tissue for up to150 days. FA analysis revealed significant reduction of the average sizes of CNV lesions in rAAV-**angiostatin**-injected eyes when compared with rAAV-lacZ-injected eyes at both 14 (P = 0.019) and 150 (P = 0.010) days after injection. Moreover, histologic analysis of CNV lesions also revealed significantly smaller lesions in rAAV-**angiostatin** -injected eyes (P = 0.004). As for adverse effects, rAAV-**angiostatin** injection did not cause inflammation or apoptosis of cells in retina and choroid.

CONCLUSIONS. This is the first report that subretinal injection of rAAV-**angiostatin** can significantly reduce the sizes of CNV lesions. This and the absence of apoptosis and inflammation in chorioretinal tissue indicate the feasibility of a gene therapy approach for treatment of CNV disease.

L3 ANSWER 24 OF 27 MEDLINE on STN DUPLICATE 2

2001462214. PubMed ID: 11507336. Corneal neovascularization. Chang J H; Gabison E E; Kato T; Azar D T. (Schepens Eye Research Institute and the Massachusetts Eye and Ear Infirmary, Department of Ophthalmology, Harvard Medical School, Boston, Massachusetts 02114, USA.) Current opinion in ophthalmology, (2001 Aug) Vol. 12, No. 4, pp. 242-9. Ref: 102. Journal code: 9011108. ISSN: 1040-8738. Pub. country: United States. Language: English.

AB Corneal neovascularization (NV) is a sight-threatening condition usually associated with inflammatory or infectious disorders of the ocular surface. It has been shown in the field of cancer angiogenesis research that a balance exists between angiogenic factors (such as fibroblast growth factor and vascular endothelial growth factor) and anti-angiogenic molecules (such as **angiostatin**, endostatin, or pigment epithelium derived factor) in the cornea. Several inflammatory, infectious, degenerative, and traumatic disorders are associated with corneal NV, in which the balance is tilted towards angiogenesis. The

pathogenesis of corneal NV may be influenced by matrix metalloproteinases and other proteolytic enzymes. New medical and surgical treatments, including angiostatic steroids, nonsteroidal inflammatory agents, argon laser photocoagulation, and **photodynamic therapy** have been effective in animal models to inhibit corneal NV and transiently restore corneal "angiogenic privilege."

L3 ANSWER 25 OF 27 MEDLINE on STN DUPLICATE 3

2001025053. PubMed ID: 11053300. **Photodynamic therapy** using Lu-Tex induces apoptosis in vitro, and its effect is potentiated by **angiostatin** in retinal capillary endothelial cells. Renno R Z; Delori F C; Holzer R A; Gragoudas E S; Miller J W. (Laser Laboratory, Retina Service, Massachusetts Eye and Ear Infirmary. Schepens Eye Research Institute, Harvard Medical School, Boston, USA.) Investigative ophthalmology & visual science, (2000 Nov) Vol. 41, No. 12, pp. 3963-71. Journal code: 7703701. ISSN: 0146-0404. Pub. country: United States. Language: English.

AB PURPOSE: To examine the effect of combining **angiostatin** with **photodynamic therapy** (PDT) using Lutetium Texaphyrin (Lu-Tex; Alcon, Fort Worth, TX) as a photosensitizer in bovine retinal capillary endothelial (BRCE) and retinal pigment epithelial (RPE) cells and to determine the mode of PDT-induced cell death in these cell lines. METHODS: Cultured BRCE and RPE cells were incubated with **angiostatin** (500 ng/ml) for 18 hours and subjected to Lu-Tex/PDT, using treatment parameters previously optimized (3 microgram/ml Lu-Tex for 30 minutes followed by timed irradiation at 732 nm). Cellular survival was assessed after a 1-week cellular proliferation. Data were analyzed using Student's t-test. Caspase 3 activity was monitored in cells after PDT using a fluorogenic substrate, (Asp-Glu-Val-Asp)-AFC (7-amino-4-trifluoromethyl coumarin) [DEVD-AFC], of caspase 3. After PDT, expression of Bcl-2, Bcl-x(L), Bax, and Bak was also examined in cell lysates by Western blot analysis. RESULTS: A synergistic cytotoxic effect of **angiostatin** and Lu-Tex/PDT was observed in BRCE cells at all fluences used (5, 10, and 20 J/cm(2); P </= 0.05). These findings applied only if **angiostatin** was delivered before PDT. No such interactive killing effect was observed in RPE cells. Caspase 3 activity was elevated within 10 minutes of PDT in BRCE and RPE cells and was fluence dependent. Differential modulation of Bcl-2 family members was observed after PDT in BRCE and RPE cells. CONCLUSIONS: The combination of **angiostatin** and Lu-Tex/PDT potentiates the cytotoxic effect of Lu-Tex/PDT on BRCE but not on RPE cells. This may provide a strategy to increase the selectivity of PDT in damaging capillary endothelial cells with less damage to RPE cells. Lu-Tex/PDT induces rapid caspase-dependent apoptosis in BRCE and RPE cells. Furthermore, Lu-Tex/PDT induces apoptosis through selective modulation of members of the Bcl-2 family and differs between BRCE and RPE cells.

L3 ANSWER 26 OF 27 BIOSIS COPYRIGHT (c) 2006 The Thomson Corporation on STN DUPLICATE 4

2000:250893 Document No.: PREV200000250893. **Photodynamic therapy** using Lu-Tex induces apoptosis in vitro and its effect is potentiated by **angiostatin** in retinal capillary endothelial cells. Renno, R. Z. [Reprint author]; Delori, F. C.; Holzer, R. A. [Reprint author]; Gragoudas, E. S. [Reprint author]; Miller, J. W. [Reprint author]. Retina Service, Mass Eye and Ear Inf, Boston, MA, USA. IOVS, (March 15, 2000) Vol. 41, No. 4, pp. S531. print. Meeting Info.: Annual Meeting of the Association in Vision and Opthalmology. Fort Lauderlade, Florida, USA. April 30-May 05, 2000. Association for Research in Vision and Ophthalmology. Language: English.

L3 ANSWER 27 OF 27 EMBASE COPYRIGHT (c) 2006 Elsevier B.V. All rights reserved on STN

2000173437 EMBASE Psoriasis: A view for the year 2000. Ellis C.N.; Barker J.N.W.N.. Dr. C.N. Ellis, Department of Dermatology, University of

Michigan, Ann Arbor, MI, United States. Current Problems in Dermatology Vol. 12, No. 2, pp. 45-50 2000.
Refs: 8.
ISSN: 1040-0486. CODEN: APDEBX
Pub. Country: United States. Language: English.
ED Entered STN: 20000531
DATA NOT AVAILABLE FOR THIS ACCESSION NUMBER

=> s l1 and anti-VEGF
L6 32 L1 AND ANTI-VEGF

=> dup remove l6
PROCESSING COMPLETED FOR L6
L7 23 DUP REMOVE L6 (9 DUPLICATES REMOVED)

=> d l7 1-23 cbib abs

L7 ANSWER 1 OF 23 MEDLINE on STN DUPLICATE 1
2006100538. PubMed ID: 16341677. [Modern pharmacotherapy of age-related macular degeneration]. Moderne Arzneimitteltherapie der altersabhangigen Makuladegeneration. Holz F G; Helb H M; Bindewald-Wittich A; Scholl H P N. (Universitats-Augenklinik, Bonn.) Der Internist, (2006 Feb) Vol. 47, No. 2, pp. 192-8. Journal code: 0264620. ISSN: 0020-9554. Pub. country: Germany: Germany, Federal Republic of. Language: German.
AB Age-related macular degeneration (AMD) is now the most common cause for blind registration in all developed countries. Epidemiologic data indicate that there are 4.5 mio affected in Germany with constant increase in incidence and prevalence with subsequent considerable health economic implications. Late manifestations of the disease result in the inability to read and to perform daily tasks. Therefore, there is an urgent need for efficacious prophylactic and therapeutic measures to prevent irreversible loss of central vision. Based on a better understanding of the underlying molecular mechanisms new therapeutic approaches have been brought forward and expand previous approaches such as thermal laser surgery or **photodynamic therapy.** Repeated intravitreal injection of **anti-VEGF** (vascular endothelial growth factor) agents as well as cosrticosteroids have a beneficial effect on growth and permeability of neovascular membranes. The risk for progression from early to late stages of AMD can be reduced with certain antioxidative preparations (AREDS medication) in presence of defined funduscopic signs. Early diagnosis is key for all currently availabe interventions since a beneficial effect can only be achieved in early stages of the disease process.

L7 ANSWER 2 OF 23 CAPLUS COPYRIGHT 2006 ACS on STN
2005:160811 Document No. 142:254653 Methods and compositions for treating wet macular degeneration with anti-vascular endothelial growth factor. Guyer, David R.; O'Shaughnessy, Denis (USA). U.S. Pat. Appl. Publ. US 2005043220 A1 20050224, 18 pp., Cont.-in-part of U.S. Ser. No. 291,091. (English). CODEN: USXXCO. APPLICATION: US 2004-928533 20040827. PRIORITY: US 2002-291091 20021108; US 2003-PV498746 20030828.
AB This invention relates to methods of treating age-related macular degeneration (AMD). In particular, this invention provides methods of treating all forms of wet, age-related macular degeneration. The method of the invention is directed to the administration of an anti-vascular endothelial growth factor (**anti-VEGF**) compound to treat wet AMD. Patients with subfoveal choroidal neovascularization secondary to AMD were treated with 100 μL intravitreal injections of EYE001 on three occasions at 28 day intervals.

L7 ANSWER 3 OF 23 CAPLUS COPYRIGHT 2006 ACS on STN
2005:1297305 Document No. 144:168255 Wet age-related macular degeneration. Kulkarni, Amol D.; Kuppermann, Baruch D. (Department of Ophthalmology, University of California, Irvine, Irvine, CA, 92697, USA). Advanced Drug

Delivery Reviews, 57(14), 1994-2009 (English) 2005. CODEN: ADDREP. ISSN: 0169-409X. Publisher: Elsevier B.V..

AB A review. Age-related macular degeneration (AMD) is the leading cause of irreversible visual loss in industrialized nations for those age 65 and above. The majority of patients with severe visual loss suffer from the wet form of AMD wherein there is choroidal neovascularization (CNV) and associated manifestations such as retinal pigment epithelial detachment, subretinal hemorrhages, and fibrovascular disciform scarring. The main focus on understanding the pathogenesis of CNV has been on the hypothesis that the diffuse thickening of Bruch's membrane predisposes it to develop cracks and in-growth of new vessels from choriocapillaries with associated low-grade inflammatory response. Currently, three types of treatments (laser photocoagulation, **photodynamic therapy**, and anti-Vascular Endothelial Growth Factor (VEGF) therapy) have been demonstrated to limit or delay loss of vision in patients. Only a minority of cases show stabilization of vision and a small proportion of cases show significant improvement in vision. This highlights the need for more and better pharmacol. or other interventions, with the goal of lowering recurrence rates and preventing the development of CNV in order to achieve better functional outcomes.

L7 ANSWER 4 OF 23 SCISEARCH COPYRIGHT (c) 2006 The Thomson Corporation on STN

2005:1088761 The Genuine Article (R) Number: 977IV. Emerging biological therapies for age-related macula degeneration. Constable I (Reprint); Shen W Y; Rakoczy E. Univ Western Australia, Ctr Ophthalmol & Visual Sci, Lions Eye Inst, 2 Verdun St, Nedlands, WA 6009, Australia (Reprint); Univ Western Australia, Ctr Ophthalmol & Visual Sci, Lions Eye Inst, Nedlands, WA 6009, Australia. ijc@cyllene.uwa.edu.au. EXPERT OPINION ON BIOLOGICAL THERAPY (OCT 2005) Vol. 5, No. 10, pp. 1373-1385. ISSN: 1471-2598. Publisher: ASHLEY PUBLICATIONS LTD, TELEPHONE HOUSE, 69-77 PAUL STREET, LONDON EC2A 4LQ, ENGLAND. Language: English.

ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB Age-related macular degeneration (AMD) has emerged as the dominant cause of irretrievable visual loss in most developed countries achieving increasing longevity. The major cause of rapid and severe visual loss is the development of choroidal neovascularisation under the macula (exudative or wet AMD). Physical treatments, especially thermal laser and **photodynamic therapy** following intravenous verteporfin, have made statistically significant but modest progress in limiting visual loss, whereas surgical translocation of the macula and even light or electrically sensitive retinal implants are spectacular, but likely to only ever benefit a few. Intravitreal fine needle injections and slow release implants of steroid derivatives have opened new areas for investigation. The blocking of endothelial receptors for vascular endothelial growth factor by RNA-based aptamer or immune-protected antibody fragments has been the subject of intensive scientific development and large scale clinical trials. This approach may expand the range of AMD patients amenable to treatment. Additional therapeutic gains await measures to modify photoreceptor cell loss and subretinal fibrosis involving the retinal pigment epithelium as well as prevention or treatment for pigment epithelial detachment. Epidemiological associations with smoking and diet, and antioxidant dietary supplements offer important strategies for prevention.

L7 ANSWER 5 OF 23 BIOSIS COPYRIGHT (c) 2006 The Thomson Corporation on STN

2005:246064 Document No.: PREV200510027731. Age-dependent macula degeneration: The results of combination treatment therapy. Kaulen, Hildegard. DMW Deutsche Medizinische Wochenschrift, (APR 8 2005) Vol. 130, No. 14, pp. 866.
CODEN: DDMWDF. ISSN: 0012-0472. Language: German.

L7 ANSWER 6 OF 23 SCISEARCH COPYRIGHT (c) 2006 The Thomson Corporation on STN

2005:587667 The Genuine Article (R) Number: 932QA. Pegaptanib sodium for the

treatment of neovascular age-related macular degeneration. Moshfeghi A A; Puliafito C A (Reprint). Univ Miami, Miller Sch Med, Dept Ophthalmol, Bascom Palmer Eye Inst, 900 NW 17th St, Miami, FL 33136 USA (Reprint); Univ Miami, Miller Sch Med, Dept Ophthalmol, Bascom Palmer Eye Inst, Miami, FL 33136 USA. cpuliafito@med.miami.edu. EXPERT OPINION ON INVESTIGATIONAL DRUGS (MAY 2005) Vol. 14, No. 5, pp. 671-682. ISSN: 1354-3784. Publisher: ASHLEY PUBLICATIONS LTD, UNITEC HOUSE, 3RD FL, 2 ALBERT PLACE, FINCHLEY CENTRAL, LONDON N3 1QB, ENGLAND. Language: English.
ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB This article reviews pegaptanib sodium, a compound developed by Eyetech Pharmaceuticals Inc. and Pfizer Inc., for the treatment of neovascular age-related macular degeneration (AMD). Traditional treatment approaches to neovascular AMD have included destructive therapies such as thermal laser photocoagulation and **photodynamic therapy** ; the use of pegaptanib sodium heralds a new treatment approach that is a non-destructive therapy based on the inhibition of vascular endothelial growth factor activity in the eye. This diminishes the neovascular drive in the pathologically hyperpermeable state of the diseased eye. Pegaptanib sodium is one of the first therapeutics belonging to the class of compounds known as aptamers. The chemistry, mechanism of action, pharmacokinetics and rationale for the clinical use of the drug are reviewed. The article highlights and summarises the results of the multi-centre, randomised, sham-controlled clinical trials with pegaptanib sodium to treat subfoveal choroidal neovascularisation in AMD. In addition, the safety profile is reviewed.

L7 ANSWER 7 OF 23 EMBASE COPYRIGHT (c) 2006 Elsevier B.V. All rights reserved on STN

2005550667 EMBASE Anti-macular degeneration agents. Rothen M.; Jablon E.; Monares G.; Fontal M.R.; Alfaro III D.V.. Dr. D.V. Alfaro III, Carolina Foundation for Macula Research and Education, Charleston, SC, United States. dralfaro@direcway.com. Ophthalmology Clinics of North America Vol. 18, No. 4, pp. 561-567 2005.
Refs: 44.
ISSN: 0896-1549. CODEN: OCNAF2
S 0896-1549(05)00096-9. Pub. Country: United States. Language: English. Summary Language: English.

ED Entered STN: 20060106

AB **Anti-VEGF** therapy is a promising new avenue for the treatment of ocular neovascular diseases. Early preclinical data and recent clinical data support the efficacy and safety of several novel **anti-VEGF** for NVAMD. Whether these novel biologics are used on their own, in combination with previously available therapies, or with newly developing therapies, they represent a new avenue in treatment. These agents are highly selective in their targeted approaches, and when administered appropriately, offer treatment with minimal damage to retinal tissue. In the future, biotherapeutic agents will certainly play a powerful role in the treatment of human choroidal neovascular membrane formation.

L7 ANSWER 8 OF 23 EMBASE COPYRIGHT (c) 2006 Elsevier B.V. All rights reserved on STN

2005304057 EMBASE Targeting angiogenesis, the underlying disorder in neovascular age-related macular degeneration. Ng E.W.M.; Adamis A.P.. Dr. A.P. Adamis, Eyetech Pharmaceuticals, Inc., 3 Times Square, New York, NY 10036, United States. Tony.Adamis@eyetech.com. Canadian Journal of Ophthalmology Vol. 40, No. 3, pp. 352-368 2005.
Refs: 130.
ISSN: 0008-4182. CODEN: CAJOBA
Pub. Country: Canada. Language: English. Summary Language: English; French.

ED Entered STN: 20050728

AB Angiogenesis has a causal role in many diseases, including neovascular age-related macular degeneration (AMD). Identification of key regulators of angiogenesis, including vascular endothelial growth factor (VEGF),

fibroblast growth factor 2, pigment epithelium-derived growth factor, angiopoietins and extracellular matrix molecules, has facilitated the development of novel therapeutic agents that target the underlying pathological angiogenic process. Among these, VEGF serves as a "master switch" for many ocular neovascular conditions through its promotion of endothelial cell proliferation and survival, vascular permeability and ocular inflammation. Two **anti-VEGF** agents are now clinically available: bevacizumab, an antibody for metastatic colorectal cancer, and pegaptanib sodium, an aptamer for neovascular AMD. Unlike bevacizumab, which binds all VEGF isoforms, pegaptanib targets only VEGF (165), the isoform responsible for pathological ocular neovascularization and thus an ideal target for treatment of AMD. Although other therapies targeting angiogenesis in AMD are in clinical development, to date, pegaptanib is the only therapy approved by the Food and Drug Administration of the United States for the treatment of all neovascular AMD and represents a valuable addition to the hitherto limited options available for patients.

L7 ANSWER 9 OF 23 BIOSIS COPYRIGHT (c) 2006 The Thomson Corporation on STN
2006:43008 Document No.: PREV200600052209. Expression of vascular endothelial growth factor (VEGF) and effects of **anti-VEGF** treatment in the rat chorioretina after **photodynamic therapy** with verteporfin. Li, R. [Reprint Author]; Zhou, S.; Nelkenbrecher, K.; Grant, K.; Dhatt, N.; Larkham, S.; Gibbon, K.; Sanghera, J.; Wolin, M.; Margaron, P.. IOVS, (2005) Vol. 46, No. Suppl. S, pp. 343.
Meeting Info.: Annual Meeting of the Association-for-Research-in-Vision-and-Ophthalmology. Ft Lauderdale, FL, USA. May 01 -05, 2005. Assoc Res Vis & Ophthalmol.
CODEN: IOVSDA. ISSN: 0146-0404. Language: English.

AB Purpose: Therapies targeting VEGF are being developed to treat choroidal neovascularization (CNV) due to AMD and initial studies have demonstrated activity in this disease. VEGF has been reported to be up-regulated in human retina after PDT with verteporfin (Visudyne (R), Novartis AG); however, the role that VEGF plays in the posterior segment in response to PDT is still unknown. Blocking VEGF may prolong CNV closure after PDT, but an **anti-VEGF** therapy may also extend the choriocapillaris hypoperfusion noticed after PDT, which may lead to potential damage to the retina. We are interested in the combination of PDT andtherapies targeting VEGF, and specifically, how to optimally and safely applyboth therapies. We investigated the role of VEGF in the biological responses of the chorioretina to PDT using an **anti-VEGF** small interfering RNA (siRNA) in the rat eye. Here we report on the expression of VEGF in the chorioretina exposed to PDT and the impact of an **anti-VEGF** siRNA on the choriocapillaris after PDT. Methods: PDT was performed in Long Evans rats using an intravenous bolus injection of 9 mg/m(2) verteporfin followed by 25 J/cm(2) light delivered to the retina at a fluence rate of 150 mW/cm(2). A siRNA that suppressed VEGF expression in rat C6 glioma cells in vitro or, as a control, a siRNA against luciferase was intravitreally injected before or afterPDT. VEGF mRNA extracted from retinas was quantified by real-time RT-PCR. Theexpression of VEGF and VEGF receptors 1 and 2 was also evaluated by immunohistochemistry. Choriocapillaris perfusion was assessed by fluorescein angiography and histology. Results: The choriocapillaris exposed to PDT was non-perfusedfor 7-14 days under the tested regimen. Rapid up-regulation of VEGF, VEGFR1 and VEGFR2, and phosphorylation of tyrosine residues on both VEGFRs were detected by immunohistology in the retina 24 h post-PDT. An increased level of VEGF mRNA was also confirmed in the PDT-treated retinas by real-time RT-PCR. Results of experiments on the effects of siRNA on PDT-induced VEGF expression and choriocapillaris closure will be shown. Conclusions: PDT induced a temporary choriocapillaris closure which was accompanied by an up-regulation of VEGF and its receptors in the chorioretina. The impact of the **anti-VEGF** siRNA on choriocapillaris hypoperfusion after PDT is being evaluated and may provide guidance on the

clinical evaluation of the combined use of verteporfin PDT with **anti-VEGF** therapies for the treatment of CNV due to AMD.

L7 ANSWER 10 OF 23 MEDLINE on STN

2005452073. PubMed ID: 16118952. [Therapy of the wet form of age-related macular disease: the present state and perspectives]. Terapia wysiekowej postaci zwyrodnienia plamki zwiazanego z wiekiem: stan obecny i perspektywy. Figurska Malgorzata; Stankiewicz Andrzej. (Z Kliniki Okulistyki Wojskowego Instytutu Medycznego w Warszawie.) Klinika oczna, (2005) Vol. 107, No. 4-6, pp. 334-9. Ref: 24. Journal code: 0376614. ISSN: 0023-2157. Pub. country: Poland. Language: Polish.

AB Age-related macular disease (ARMD) is affecting the central part of the retina. ARMD has two major forms: the dry type and the wet type. Although wet type comprises only 15% of ARMD, it is responsible for 90% of severe visual impairment in all ARMD cases. The problem is effective treatment of ARMD, above all its wet type. Laser therapy, retina surgery, TTT and local radiotherapy did not give expected results. The aim of this article is to present modern trends of wet type ARMD therapy, including pharmacotherapy and **photodynamic therapy** (PDT) in relation to pathobiology of choroidal neovascularization (CNV). The goals of pharmacotherapy were discussed in support, that choroidal neovascularization is a dynamic evolution, which includes initiation, active inflammation and non active involution. Cellular mechanisms of **photodynamic therapy** were presented. It is necessary to accentuate that in the future it can be a combination between PDT and pharmacotherapy, which inhibits early stage mediators of all types CNV and limits inflammation attendant CNV. These therapeutic approaches ere more likely succeed and included wide spectrum of wet ARMD pathogenesis. The clinical studies show that may be soon we will treat wet form of ARMD using angiostatic steroids, **anti-VEGF** monoclonal antibodies and **anti-VEGF** aptamers.

L7 ANSWER 11 OF 23 SCISEARCH COPYRIGHT (c) 2006 The Thomson Corporation on STN

2005:635626 The Genuine Article (R) Number: 911CZ. Expression of vascular endothelial growth factor (VEGF) and effects of **anti-VEGF** treatment in the rat chorioretina after **photodynamic therapy** with verteporfin. Li R (Reprint); Zhou S; Nelkenbrecher K; Grant K; Dhatt N; Larkham S; Gibbon K; Sanghera J; Wolin M; Margaron P.. INVESTIGATIVE OPHTHALMOLOGY & VISUAL SCIENCE (2005) Vol. 46, Supp. [S], pp. U61-U61. MA 343. ISSN: 0146-0404. Publisher: ASSOC RESEARCH VISION OPHTHALMOLOGY INC, 12300 TWINBROOK PARKWAY, ROCKVILLE, MD 20852-1606 USA. Language: English.

L7 ANSWER 12 OF 23 CAPLUS COPYRIGHT 2006 ACS on STN

2004:775873 Document No. 141:254622 **Photodynamic therapy** comprising benzoporphyrin and **anti-VEGF** antibody conjugates for ocular diseases. Glickman, Randolph D.; Mayo, George L.; McKinnon, Stuart J.; Melendez, Robert F.; Kumar, Neeru C. (Board of Regents, the University of Texas System, USA). PCT Int. Appl. WO 2004080284 A2 20040923, 45 pp. DESIGNATED STATES: W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG, TR. (English). CODEN: PIXXD2. APPLICATION: WO 2004-US6985 20040308. PRIORITY: US 2003-PV452655 20030307.

AB The present invention provides photosensitizer-antibody conjugates, methods for making such conjugates and uses as **photodynamic therapy** in treating ocular diseases. Specifically, the method of treating a subject with ocular disease comprises: administering to the subject a conjugate of a benzoporphyrin and an **anti-VEGF**

antibody and irradiating the subject with light. The symptoms of the ocular disease are reduced as compared to a control lacking the conjugate.

L7 ANSWER 13 OF 23 CAPLUS COPYRIGHT 2006 ACS on STN
2004:354717 Document No. 140:352747 **Photodynamic therapy** for ocular neovascularization. Freeman, William R. (The Regents of the University of California, USA). PCT Int. Appl. WO 2004034889 A2 20040429, 38 pp. DESIGNATED STATES: W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG, TR. (English). CODEN: PIXXD2. APPLICATION: WO 2003-US33365 20031020. PRIORITY: US 2002-2002/PV419883 20021018.

AB Method, apparatuses and systems are provided for the photodynamic treatment of feeder vessels associated with aberrant choroidal neovasculature.

L7 ANSWER 14 OF 23 MEDLINE on STN
2003229467. PubMed ID: 12750101. Anti-vascular endothelial growth factor therapy for subfoveal choroidal neovascularization secondary to age-related macular degeneration: phase II study results. Anonymous. (Eyetech Study Group.) Ophthalmology, (2003 May) Vol. 110, No. 5, pp. 979-86. Journal code: 7802443. ISSN: 0161-6420. Pub. country: United States. Language: English.

AB PURPOSE: There is evidence to suggest that anti-vascular endothelial growth factor (**anti-VEGF**) therapy may be useful in treating ocular neovascularization. A phase IA single intravitreal injection study of **anti-VEGF** therapy for patients with subfoveal choroidal neovascularization (CNV) secondary to age-related macular degeneration (AMD) revealed a good safety profile. We performed a phase II multiple injection study of **anti-VEGF** therapy with and without **photodynamic therapy** for patients with subfoveal CNV secondary to AMD to determine the safety profile of multiple injection therapy. DESIGN: A phase II multiple-dose safety study. PARTICIPANTS/METHODS: Twenty-one patients were treated with intravitreal injection with and without **photodynamic therapy**. MAIN OUTCOME MEASURES: Clinical evidence of toxicity and complications. RESULTS: No drug-related serious adverse events were revealed. Ophthalmic evaluation revealed that 87.5% of patients who received the **anti-VEGF** aptamer alone showed stabilized or improved vision 3 months after treatment and that 25% of eyes demonstrated a 3 line or greater improvement in vision on the Early Treatment of Diabetic Retinopathy Study chart during this period. A 60% 3 line gain at 3 months was noted in patients who received both the **anti-VEGF** aptamer and **photodynamic therapy**. CONCLUSIONS: **Anti-VEGF** therapy is a promising treatment for various forms of ocular neovascularization, including AMD. Multiple intravitreal injections of the **anti-VEGF** aptamer were well tolerated in this phase II study. Further clinical trials are necessary to demonstrate the efficacy and long-term safety of **anti-VEGF** therapy for AMD.

L7 ANSWER 15 OF 23 CAPLUS COPYRIGHT 2006 ACS on STN
2003:717753 Document No. 139:226552 Methods for treating ocular neovascular diseases. Guyer, David R. (USA). U.S. Pat. Appl. Publ. US 2003171320 A1 20030911, 17 pp. (English). CODEN: USXXCO. APPLICATION: US 2002-291091 20021108. PRIORITY: US 2001-2001/PV332304 20011109.

AB Disclosed herein are methods for treating ocular neovascular disease using **anti-VEGF** therapy in combination with a second therapy that inhibits the development of ocular neovascularization or destroys abnormal blood vessels in the eye, such as **photodynamic therapy**.

L7 ANSWER 16 OF 23 CAPLUS COPYRIGHT 2006 ACS on STN
2003:938036 Document No. 141:128566 Antibody-targeted **photodynamic therapy**. Mayo, George L.; Melendez, Robert F.; Kumar, Neeru; McKinnon, Stuart J.; Glickman, Randolph D. (Department of Ophthalmology, University of Texas Health Science Center at San Antonio, San Antonio, TX, USA). American Journal of Ophthalmology, 136(6), 1151-1152 (English) 2003. CODEN: AJOPAA. ISSN: 0002-9394. Publisher: Elsevier Science Inc..
AB The purpose was to assess the feasibility of conjugation of verteporfin (Visudyne, Parkedale Pharmaceuticals, Rochester, Minnesota, USA) to antibody against vascular endothelial growth factor. Rabbit antimouse vascular endothelial growth factor polyclonal antibody was conjugated to verteporfin. Fluorescence excitation-emission spectra of verteporfin and conjugate were examined Vascular endothelial growth factor-expressing murine endothelial cells were incubated with saline, verteporfin, or conjugate, followed by laser exposure or no laser exposure. Cell viability at 1 and 24 h was assessed via trypan blue exclusion. Results were analyzed by two-way anal. of variance with replication and the Bonferroni multiple comparison test. The fluorescence excitation-emission spectrum of the conjugate was similar to that of verteporfin. After laser exposure, cell viability in conjugate-treated cells was reduced to 6% at 1 h ($P < .0001$) and to 4% at 24 h ($P < .0001$), compared with approx. 40% in nonlaser-exposed, conjugate-treated cells. The cytotoxicity in the conjugate-treated cells was higher than in verteporfin-treated cells exposed to laser, although the difference did not reach statistical significance. The conjugation of verteporfin to polyclonal antibody is possible without the loss of its photosensitizing properties. Conjugated verteporfin destroys cellular targets at least as effectively as verteporfin alone.

L7 ANSWER 17 OF 23 EMBASE COPYRIGHT (c) 2006 Elsevier B.V. All rights reserved on STN DUPLICATE 2
2003193265 EMBASE Anti-vascular endothelial growth factor therapy for subfoveal choroidal neovascularization secondary to age-related macular degeneration: Phase II study results. Guyer D.R.; Fish G.; Haller J.A.; Ho A.C.; Klein M.; Loewenstein J.; Martin D.; Orth D.; Rosen R.B.; Sanislo S.; Schwartz S.D.; Singerman L.J.; Williams G.. Dr. D.R. Guyer, Eyetech Pharmaceuticals, 500 Seventh Avenue, New York, NY 10018, United States.
Ophthalmology Vol. 110, No. 5, pp. 979-986 1 May 2003.
Refs: 24.
ISSN: 0161-6420. CODEN: OPHTDG
Pub. Country: United States. Language: English. Summary Language: English.
ED Entered STN: 20030529
AB Purpose: There is evidence to suggest that anti-vascular endothelial growth factor (**anti-VEGF**) therapy may be useful in treating ocular neovascularization. A phase IA single intravitreal injection study of **anti-VEGF** therapy for patients with subfoveal choroidal neovascularization (CNV) secondary to age-related macular degeneration (AMD) revealed a good safety profile. We performed a phase II multiple injection study of **anti-VEGF** therapy with and without **photodynamic therapy** for patients with subfoveal CNV secondary to AMD to determine the safety profile of multiple injection therapy. Design: A phase II multiple-dose safety study. Participants/Methods: Twenty-one patients were treated with intravitreal injection with and without **photodynamic therapy**. Main Outcome Measures: Clinical evidence of toxicity and complications. Results: No drug-related serious adverse events were revealed. Ophthalmic evaluation revealed that 87.5% of patients who received the **anti-VEGF** aptamer alone showed stabilized or improved vision 3 months after treatment and that 25% of eyes demonstrated a 3 line or greater improvement in vision on the Early Treatment of Diabetic Retinopathy Study chart during this period. A 60% 3 line gain at 3 months was noted in patients who received both the **anti-VEGF** aptamer and **photodynamic therapy**. Conclusions: **Anti-VEGF** therapy is a

promising treatment for various forms of ocular neovascularization, including AMD. Multiple intravitreal injections of the **anti-VEGF** aptamer were well tolerated in this phase II study. Further clinical trials are necessary to demonstrate the efficacy and long-term safety of **anti-VEGF** therapy for AMD. .COPYRGT. 2003 by the American Academy of Ophthalmology.

L7 ANSWER 18 OF 23 MEDLINE on STN DUPLICATE 3

2003509551. PubMed ID: 14586234. [Alternative therapies for choroidal neovessels resulting from age-related macular degeneration]. Therapeutiques alternatives des neovaisseaux choroidiens de la degenerescence maculaire liee a l'age. Soubrane G; Souied E; Haddad W; Razavi S; Roquet W; Coscas G. (Clinique Ophtalmologique Universitaire de Creteil, Universite Paris-XII, 40, avenue de Verdun, 94010 Creteil.. gisele.soubrane@chicreteil.fr) . Journal francais d'ophtalmologie, (2003 Oct) Vol. 26, No. 8, pp. 876-8. Ref: 16. Journal code: 7804128. ISSN: 0181-5512. Pub. country: France. Language: French.

AB Classic neovessels (CNVs) identified on fluorescein angiography may benefit from thermal laser photocoagulation when sparing the fovea. If they extend into it, **photodynamic therapy** may halt the natural progression to a central scotoma. Occult CNVs, when subfoveal, may benefit from **photodynamic therapy** when isolated (not associated with classic CNV or with a pigment epithelium detachment). A number of therapeutic approaches are being evaluated in order to diversify the therapeutic choices available for treatment of CNVs. Transpupillary thermotherapy, which causes a limited increase in retinal temperature, could produce a sclerosis of occult isolated CNV. This approach has shown interesting results in pilot studies but also carries a risk for iatrogenic effects. The American randomized clinical trial currently under way will provide an evaluation of this treatment. An antiangiogenic therapy currently in progress is studying anecortave acetate and another is investigating **anti-VEGF** compounds. Anecortave acetate, which demonstrated its angiostatic activity in experimental models as well as in a phase II study, is now in a worldwide randomized clinical trial. The **anti-VEGF** molecules (antibodies and oligonucleotides) have shown very interesting preliminary results and are being evaluated in a large number of patients. Finally, a preventive therapy consisting of oral supplementation with antioxidants (vitamins C, E, and A) and zinc is a major step forward, providing the possibility of a real and effective prevention of the complications of age-related maculopathy.

L7 ANSWER 19 OF 23 SCISEARCH COPYRIGHT (c) 2006 The Thomson Corporation on STN

2003:825760 The Genuine Article (R) Number: 723QL. Ranibizumab - Treatment of age-related macular degeneration humanized monoclonal **anti-VEGF** antibodiy angiogenesis inhibitor. Sorbera L A (Reprint); Leeson P A; Bayes M. Prous Sci, POB 540, Barcelona 08080, Spain (Reprint); Prous Sci, Barcelona 08080, Spain. DRUGS OF THE FUTURE (JUN 2003) Vol. 28, No. 6, pp. 541-545. ISSN: 0377-8282. Publisher: PROUS SCIENCE, SA, PO BOX 540, PROVENZA 388, 08025 BARCELONA, SPAIN. Language: English.

ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB Wet type or exudative age-related macular degeneration (AMD) is a complex and multifactorial disease which affects older individuals and is characterized by subretinal or choroidal neovascularization (CNV) evident under the retina and macula. These new, abnormal blood vessels may bleed or leak fluid, causing the macula to bulge and lift up which results in rapid and severe distortion or destruction of central vision. Overexpression of vascular endothelial growth factors (VEGFs) and their receptors has been found to be associated with increased microvascular permeability in the eye. Thus, antiangiogenic therapy using VEGF as a target may be a selective and effective treatment option for the wet form of AMD. Ranibizumab is the antigen-binding fragment of a recombinant humanized monoclonal antibody directed toward VEGF that can penetrate the internal limiting membrane to access the subretinal space. Ranibizumab

was chosen for further development as a treatment for the wet form of AMD.

L7 ANSWER 20 OF 23 EMBASE COPYRIGHT (c) 2006 Elsevier B.V. All rights reserved on STN DUPLICATE 4

2002432788 EMBASE Pegaptanib sodium: Treatment of age-related macular degeneration treatment of diabetic retinopathy **anti-VEGF** aptamer. Sorbera L.A.; Leeson P.A.; Bayes M.. L.A. Sorbera, Prous Science, P.O. Box 540, 08080 Barcelona, Spain. Drugs of the Future Vol. 27, No. 9, pp. 841-845 1 Sep 2002.
Refs: 26.
ISSN: 0377-8282. CODEN: DRFUD4
Pub. Country: Spain. Language: English. Summary Language: English.

ED Entered STN: 20021219

AB Exudative age-related macular degeneration (AMD) and diabetic macular edema (DME) are the leading causes of vision loss in the elderly and diabetics, respectively, in the Western world. Although photocoagulation and **photodynamic therapy** are indicated for these pathologies, recurrence is exceptionally high. Thus, the search continues for a more effective treatment for these disorders. Vascular endothelial growth factor (VEGF) is a cytokine involved in angiogenesis and necessary for normal vascular development. However, it has also been implicated in several pathologies such as AMD, DME and choroidal neovascularization (CNV) where patients display high intraocular VEGF levels. Thus, **anti-VEGF** therapy is an attractive therapeutic option for these diseases. One such **anti-VEGF** agent is the pegylated aptamer pegaptanib sodium. Pegaptanib specifically binds with high affinity to VEGF(165), the major soluble human VEGF isoform, and has been shown to potently inhibit blood vessel growth and block neovascularization in preclinical models. It has been chosen for further development for the treatment of AMD and DME and is the first aptamer to reach human clinical testing.

L7 ANSWER 21 OF 23 BIOSIS COPYRIGHT (c) 2006 The Thomson Corporation on STN

2003:154978 Document No.: PREV200300154978. **Anti-VEGF** Therapy for Subfoveal Choroidal Neovascularization Secondary to Age-related Macular Degeneration: Phase IB Results. Singerman, L. J. [Reprint Author]; EyeTech Study Group [Reprint Author]. Cleveland, OH, USA. ARVO Annual Meeting Abstract Search and Program Planner, (2002) Vol. 2002, pp. Abstract No. 2908. cd-rom.
Meeting Info.: Annual Meeting of the Association For Research in Vision and Ophthalmology. Fort Lauderdale, Florida, USA. May 05-10, 2002.
Language: English.

AB Purpose: Research suggests that anti-vascular endothelial growth factor (VEGF) therapy may be useful in the treatment of ocular neovascularization. A Phase IA study of a single intravitreal injection of **anti-VEGF** in patients with subfoveal choroidal neovascularization (CNV) secondary to age-related macular degeneration (AMD) revealed a good safety profile. To determine the safety profile of multiple-injection therapy, we performed a Phase IB study of multiple injections of **anti-VEGF**, with or without **photodynamic therapy** (PDT), in patients with subfoveal CNV secondary to AMD. Methods: A Phase IB multiple-dose study of intravitreal injection of the drug, with or without PDT, was performed in 21 patients with subfoveal CNV secondary to AMD. Results: There were no significant safety issues related to the drug. Ophthalmic evaluation 3 months after treatment showed that 87.5% of patients who received only the **anti-VEGF** aptamer showed stable or improved vision and that 25% demonstrated a 3-line or greater improvement in vision on the ETDRS chart. A 3-line gain at 3 months was observed in 60% of patients who received both the **anti-VEGF** aptamer and **photodynamic therapy.** Conclusion: **Anti-VEGF** therapy is a promising treatment of neovascularization secondary to various ocular diseases, including AMD. In this Phase IB study, multiple intravitreal injections of the **anti-VEGF**

aptamer were well tolerated, and visual results were very encouraging. Further clinical trials are required, and a Phase III study to evaluate the efficacy and long-term safety of this treatment is currently underway at 115 centers in the USA and abroad.

L7 ANSWER 22 OF 23 BIOSIS COPYRIGHT (c) 2006 The Thomson Corporation on STN

2003:154690 Document No.: PREV200300154690. rhuFabV2 (an **Anti-VEGF** Antibody Fragment) in Neovascular AMD: Safety and Tolerability of Multiple Intravitreal Injections. Heier, J. S. [Reprint Author]; Greene, W. L.; rhuFabV2 Study Group. Ophthalmic Consultants of Boston, Boston, MA, USA. ARVO Annual Meeting Abstract Search and Program Planner, (2002) Vol. 2002, pp. Abstract No. 2520. cd-rom.
Meeting Info.: Annual Meeting of the Association For Research in Vision and Ophthalmology. Fort Lauderdale, Florida, USA. May 05-10, 2002.
Language: English.

AB Purpose: To investigate the safety, tolerability, and biologic activity of rhuFabV2, a monoclonal antibody fragment directed against VEGF, when administered as a series of four intravitreal injections to subjects with neovascular AMD. Methods: Open-label, randomized, controlled study. Up to 60 subjects will be enrolled (4:1 rhuFab V2:Usual Care) in up to 2 dose groups: 300mg and 500mg every 28 days (4 injections total). Subjects may cross over to Usual Care or rhuFab V2 treatment for 12 weeks after the initial study period. Eligible subjects have one of the three following characteristics: 1) predominately occult CNV with some amount of classic; 2) a PDT-eligible lesion (predominately classic subfoveal CNV); or 3) an active lesion after treatment with PDT. All subjects undergo ETDRS visual acuity testing, ophthalmologic examination, fluorescein angiography, and fundus photography at baseline and during treatment and follow-up. Endpoints investigated include visual acuity, adverse events (ocular and non-ocular) and markers of biologic activity such as change in leakage from CNV and CNV size/characteristics. Results: As of 12/5/01, the 300mg dose group has been enrolled (30 subjects total). Overall, mean subject age is 73, 100% are Caucasian, and 45% are female. CNV was predominately classic in 8/30 (27%) of subjects, predominately occult in 14/30 (46%), and post-PDT in 8/30 (27%). Baseline visual acuity ranged from 20/50 to 20/500, with a median of 20/125. There have been no drug-related serious adverse events, and all subjects tolerated the injections. Conclusion: rhuFabV2 at a monthly dose of 300mg has been tolerated in this Phase Ib/II study, and rhuFabV2 is undergoing further evaluation in the management of subfoveal CNV.

L7 ANSWER 23 OF 23 BIOSIS COPYRIGHT (c) 2006 The Thomson Corporation on STN

2003:142492 Document No.: PREV200300142492. Safety and Efficacy of Intravitreal Injection of rhuFab VEGF in Combination With Verteporfin PDT on Experimental Choroidal Neovascularization. Gauthier, D. [Reprint Author]; Husain, D. [Reprint Author]; Kim, I. K. [Reprint Author]; Ezra, E. [Reprint Author]; Tsilimbaris, M. K. [Reprint Author]; Connolly, E. [Reprint Author]; Lane, A. M.; Gragoudas, E. S. [Reprint Author]; O'Neill, C. A.; Miller, J. W. [Reprint Author]. Retina Service, Angiogenesis Laboratory, Massachusetts Eye and Ear Infirmary, Boston, MA, USA. ARVO Annual Meeting Abstract Search and Program Planner, (2002) Vol. 2002, pp. Abstract No. 566. cd-rom.
Meeting Info.: Annual Meeting of the Association For Research in Vision and Ophthalmology. Fort Lauderdale, Florida, USA. May 05-10, 2002.
Language: English.

AB Purpose: To study the safety and efficacy of intravitreal injection of **anti-VEGF** antibody fragment (rhuFab VEGF) in combination with intravenous verteporfin **photodynamic therapy** (PDT) on experimental choroidal neovascularization in the monkey. Methods: Choroidal neovascularlation was induced by laser injury in both eyes of cynomolgus monkeys and followed with weekly fundus photography and fluroescein angiography. Two weeks after induction, weekly treatments were started using intravitreal injection of rhuFab VEGF or placebo and

PDT. Nine animals received intravitreal injections alternating with PDT. Six of these animals (group I) initially received intravitreal injections and were followed for 63 days. Three of these animals (group II) initially received PDT and were followed for 56 days. Two animals (group III) received injections and PDT the same day at two week intervals and were followed for 56 days. Fluorescein angiograms were graded using a masked, standardized protocol. The data were analyzed using the Stuart-Maxwell chi-square test for matched-pair analysis. Results: Three weeks after the start of treatment, 11 of 11 eyes treated with a combination of rhuFab VEGF injections and PDT showed no leakage from CNV on fluorescein angiography. This finding persisted for 6 weeks of follow-up. In those animals treated with placebo injections and PDT, 7 of 11 eyes showed no leakage from CNV, and 4 showed persistent leakage at 3 weeks. At 6 weeks, 9 of 11 eyes showed no leakage, and 2 eyes showed persistent leakage. Conclusion: Preliminary data indicate that intravitreal rhuFab VEGF in combination with verteporfin PDT causes greater reduction in angiographic leakage than PDT alone in experimental choroidal neovascularization.

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=> s (miller j?/au or gragoudas e?/au or renno r?/au)
L8       55669 (MILLER J?/AU OR GRAGOUDAS E?/AU OR RENNO R?/AU)

=> s l8 and photodynamic therapy
L9         307 L8 AND PHOTODYNAMIC THERAPY

=> s l9 and angiopoietin combination
L10          0 L9 AND ANGIOPOIETIN COMBINATION

=> s l9 and anti-VEGF combination
L11          0 L9 AND ANTI-VEGF COMBINATION

=> s l9 and angiostatin
L12         12 L9 AND ANGIOSTATIN

=> dup remove l12
PROCESSING COMPLETED FOR L12
L13           8 DUP REMOVE L12 (4 DUPLICATES REMOVED)

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L13  ANSWER 1 OF 8  SCISEARCH  COPYRIGHT (c) 2006 The Thomson Corporation  on
     STN
2003:1054374   The Genuine Article (R) Number: 709CH. Enhanced
     photodynamic therapy using angiostatin with
     verteporfin PDT in a laser-injury rat model.  Terada Y (Reprint); Michaud
     N A; Connolly E J; Lane A; Ohtsuki H; Gragoudas E S; Miller
     J W. Massachusetts Eye & Ear Infirm, Retina Serv, Angiogenesis &
     Laser Lab, Boston, MA 02114 USA; Okayama Univ, Sch Med, Okayama 700, Japan
     . INVESTIGATIVE OPHTHALMOLOGY & VISUAL SCIENCE (MAY 2003) Vol. 44, Supp.
     [1], pp. U408-U408. MA 1749. ISSN: 0146-0404. Publisher: ASSOC RESEARCH
     VISION OPHTHALMOLOGY INC, 12300 TWINBROOK PARKWAY, ROCKVILLE, MD
     20852-1606 USA. Language: English.

L13  ANSWER 2 OF 8  EMBASE  COPYRIGHT (c) 2006 Elsevier B.V. All rights
     reserved on STN
2003249645  EMBASE  Photodynamic therapy for choroidal
     neovascularization. The Jules Gonin Lecture, Montreux, Switzerland, 1
     September 2002. Miller J.W.. J.W. Miller, Angiogenesis and Laser
     Laboratories, Harvard Medical School, Massachusetts Eye and Ear Infirmary,
     Boston, MA, United States. jwmiller@meei.harvard.edu. Graefe's Archive for
     Clinical and Experimental Ophthalmology  Vol. 241, No. 4, pp. 258-262  1
     Apr 2003.
     Refs: 30.
     ISSN: 0721-832X. CODEN: GACODL
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Pub. Country: Germany. Language: English.
ED Entered STN: 20030710
AB In summary, the targeted verteporfin and verteporfin-PVA were both more efficient at CNV closure than unbound verteporfin. VEGFR2-targeted verteporfin appeared to be selective when normal retina and choroid were treated, resulting in choriocapillaris closure with minimal effect on RPE or neurosensory retina. In contrast, the verteporfin-PVA control showed non-selective retinal damage. These positive findings will be pursued further in experimental models and will hopefully warrant clinical investigation in the future. Another direction that we also wish to pursue would be to modulate the PDT response in normal and diseased tissue using factors in the apoptosis pathway, and preliminary in vitro work supports this strategy [27]. We would also like to improve drug delivery for anti-angiogenic and neuroprotective agents and towards this end have been working on a trans-scleral drug delivery approach.

L13 ANSWER 3 OF 8 BIOSIS COPYRIGHT (c) 2006 The Thomson Corporation on STN
2003:529243 Document No.: PREV200300524981. ENHANCED **PHOTODYNAMIC THERAPY** USING **ANGIOSTATIN** WITH VERTEPORFIN PDT IN A LASER - INJURY RAT MODEL. Terada, Y. [Reprint Author]; Michaud, N. A. [Reprint Author]; Connolly, E. J. [Reprint Author]; Lane, A. [Reprint Author]; Ohtsuki, H.; **Gragoudas, E. S.** [Reprint Author]; **Miller, J. W.** [Reprint Author]. Retina Service, Angiogenesis and Laser Laboratory, Mass Eye and Ear Infirmary, Boston, MA, USA. ARVO Annual Meeting Abstract Search and Program Planner, (2003) Vol. 2003, pp. Abstract No. 1749. cd-rom.
Meeting Info.: Annual Meeting of the Association for Research in Vision and Ophthalmology. Fort Lauderdale, FL, USA. May 04-08, 2003. Association for Research in Vision and Ophthalmology.
Language: English.
AB Purpose: Previous studies had shown increased cytotoxicity of verteporfin **photodynamic therapy** (PDT) combined with the anti-angiogenic drug **angiostatin** for bovine retinal microcapillary endothelium (bRME) but not for human retinal pigment epithelium (hRPE) in vitro. Here, we investigated the selectivity and the efficacy of PDT combined with **angiostatin** in vivo. Methods: Choroidal neovascular membranes (CNV) were induced in Brown-Norway rats using Argon/Dye laser. After the initial laser CNV induction, rats were treated with either **angiostatin** bolus injections intraperitoneally (12 and 24 hours before PDT) at 50 mg/kg or continuous administration of **angiostatin** through subcutaneously implanted osmotic pumps at 15mg/kg/day. Verteporfin PDT was performed at verteporfin dose of 3 or 6 mg/m2 using an irradiance of 600mW/cm2 and fluence of 10 and 25 J/cm2. Fluorescein angiograms performed 20 days after laser injury but before PDT, as well as 1 and 7 days after PDT were graded in a masked fashion using grading standards of CNV leakage. Non-parametric and parametric techniques were used to evaluate treatment effects. Results: **Angiostatin** alone did not prevent CNV growth using either model of administration. Bolus intraperitoneal administration of **angiostatin** prior to verteporfin PDT did not increase the efficacy of verteporfin PDT on CNV closure (P>.40 for differences in leakage between eyes treated with PDT vs. PDT with **angiostatin** at both timepoints and fluences).Continuous subcutaneous administration of **angiostatin** was significantly associated with CNV closure (beta=2.63, P=.002) in regression analysis adjusting for the effects of fluence. Conclusions: Continuous administration of **angiostatin** potentiated the efficacy of verteporfin PDT for CNV closure in a laser-injury rat model. Combined therapy of anti-angiogenic drugs and PDT may limit the damage to normal structure and improve PDT results.

L13 ANSWER 4 OF 8 SCISEARCH COPYRIGHT (c) 2006 The Thomson Corporation on STN
2003:955111 The Genuine Article (R) Number: 709CF. Modified verteporfin **photodynamic therapy** (PDT), PDT combined with

angiostatin in vitro and in vivo. Terada Y (Reprint); Zacks D N; Connolly E J; Michaud N; **Gragoudas E S**; **Miller J W.** Harvard Univ, Sch Med, Massachusetts Eye & Ear Infirm, Retina Serv, Angiogenesis & Laser Res Lab, Boston, MA USA. INVESTIGATIVE OPHTHALMOLOGY & VISUAL SCIENCE (MAY 2002) Vol. 43, Supp. [1], pp. U114-U114. MA 574. ISSN: 0146-0404. Publisher: ASSOC RESEARCH VISION OPHTHALMOLOGY INC, 12300 TWINBROOK PARKWAY, ROCKVILLE, MD 20852-1606 USA. Language: English.

L13 ANSWER 5 OF 8 BIOSIS COPYRIGHT (c) 2006 The Thomson Corporation on STN
2003:142500 Document No.: PREV200300142500. Modified Verteporfin **Photodynamic Therapy** (PDT), PDT Combined With **Angiostatin** In Vitro and In Vivo. Terada, Y. [Reprint Author]; Zacks, D. N. [Reprint Author]; Connolly, E. J. [Reprint Author]; Michaud, N. [Reprint Author]; **Gragoudas, E. S.** [Reprint Author]; **Miller, J. W.** [Reprint Author]. Angiogenesis and Laser Research Laboratory, Retina Service, Mass Eye and Ear Infirmary, Harvard Medical School, Boston, MA, USA. ARVO Annual Meeting Abstract Search and Program Planner, (2002) Vol. 2002, pp. Abstract No. 574. cd-rom. Meeting Info.: Annual Meeting of the Association For Research in Vision and Ophthalmology. Fort Lauderdale, Florida, USA. May 05-10, 2002. Language: English.

AB Purpose: To investigate the selectivity and the efficacy of PDT combined with the anti-angiogenic drug **angiostatin** in vitro and in vivo. Methods: (in vitro) Human retinal pigment epithelial (hRPE) and bovine retinal microvascular endothelial cells (bRME) were maintained in conditioned media. Verteporfin PDT was performed on cells with or without prior exposure to 100ng/mL of **angiostatin.** Cellular survival was assessed at 24 hours after PDT. (in vivo) Choroidal neovascular membranes (CNV) were induced in Brown-Norway rats using Argon/Dye laser. Four groups were studied: 1. control rats (placebo), 2. **angiostatin** alone (50mg/kg) 1 and 2 weeks after CNV induction, 3. verteporfin PDT alone and 4. PDT plus 50mg/kg of **angiostatin** 12 and 24 hours prior to PDT at verteporfin dose of 3mg/m2 using an irradiance of 600mW/cm2 and fluence of 10 and 25 J/cm2. Fluorescein angiography was performed at 3 and 4 weeks after CNV induction and at 24 hours and 7 days after PDT, and graded in a masked standardized fashion. Results: In vitro results showed increased cytotoxicity for bRME but for hRPE when **angiostatin** was combined with verteporfn PDT. In vivo results showed that **angiostatin** alone did not prevent CNV, and there was no increased efficacy when **angiostatin** was administered prior to verteporfin PDT at the doses tested. Conclusion: **Angiostatin** potentiated the efficacy of verteporfin PDT for microvascular endothelium. However, in vivo **angiostatin** did not appear to potentiate the effect of verteporfin PDT on CNV at the doses tested.

L13 ANSWER 6 OF 8 CAPLUS COPYRIGHT 2006 ACS on STN
2001:597738 Document No. 135:149263 Methods and compositions for treating condition of the eye. **Miller, Joan W.**; **Gragoudas, Evangelos S.**; **Renno, Reem Z.** (Massachusetts Eye and Ear Infirmary, USA). PCT Int. Appl. WO 2001058240 A2 20010816, 46 pp. DESIGNATED STATES: W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, US, UG, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG, TR. (English). CODEN: PIXXD2. APPLICATION: WO 2001-US4231 20010209. PRIORITY: US 2000-PV181641 20000210.

AB Provided are methods and compns. for the **photodynamic therapy** (PDT) of ocular conditions characterized by the presence of unwanted choroidal neovasculature, for example, neovascular age-related macular degeneration. The selectivity and sensitivity of the PDT method can be enhanced by combining the PDT with an anti-angiogenesis factor, for

example, **angiostatin** or endostatin, or with an apoptosis-modulating factor. Furthermore, the selectivity and sensitivity of the PDT may be further enhanced by coupling a targeting moiety to the photosensitizer so as to target the photosensitizer to choroidal neovasculature.

L13 ANSWER 7 OF 8 MEDLINE on STN DUPLICATE 1
2001025053. PubMed ID: 11053300. **Photodynamic therapy** using Lu-Tex induces apoptosis in vitro, and its effect is potentiated by **angiostatin** in retinal capillary endothelial cells. **Renno R Z**; Delori F C; Holzer R A; **Gragoudas E S**; **Miller J W**. (Laser Laboratory, Retina Service, Massachusetts Eye and Ear Infirmary. Schepens Eye Research Institute, Harvard Medical School, Boston, USA.) Investigative ophthalmology & visual science, (2000 Nov) Vol. 41, No. 12, pp. 3963-71. Journal code: 7703701. ISSN: 0146-0404. Pub. country: United States. Language: English.

AB PURPOSE: To examine the effect of combining **angiostatin** with **photodynamic therapy** (PDT) using Lutetium Texaphyrin (Lu-Tex; Alcon, Fort Worth, TX) as a photosensitizer in bovine retinal capillary endothelial (BRCE) and retinal pigment epithelial (RPE) cells and to determine the mode of PDT-induced cell death in these cell lines. METHODS: Cultured BRCE and RPE cells were incubated with **angiostatin** (500 ng/ml) for 18 hours and subjected to Lu-Tex/PDT, using treatment parameters previously optimized (3 microgram/ml Lu-Tex for 30 minutes followed by timed irradiation at 732 nm). Cellular survival was assessed after a 1-week cellular proliferation. Data were analyzed using Student's t-test. Caspase 3 activity was monitored in cells after PDT using a fluorogenic substrate, (Asp-Glu-Val-Asp)-AFC (7-amino-4-trifluoromethyl coumarin) [DEVD-AFC], of caspase 3. After PDT, expression of Bcl-2, Bcl-x(L), Bax, and Bak was also examined in cell lysates by Western blot analysis. RESULTS: A synergistic cytotoxic effect of **angiostatin** and Lu-Tex/PDT was observed in BRCE cells at all fluences used (5, 10, and 20 J/cm(2); P </= 0.05). These findings applied only if **angiostatin** was delivered before PDT. No such interactive killing effect was observed in RPE cells. Caspase 3 activity was elevated within 10 minutes of PDT in BRCE and RPE cells and was fluence dependent. Differential modulation of Bcl-2 family members was observed after PDT in BRCE and RPE cells. CONCLUSIONS: The combination of **angiostatin** and Lu-Tex/PDT potentiates the cytotoxic effect of Lu-Tex/PDT on BRCE but not on RPE cells. This may provide a strategy to increase the selectivity of PDT in damaging capillary endothelial cells with less damage to RPE cells. Lu-Tex/PDT induces rapid caspase-dependent apoptosis in BRCE and RPE cells. Furthermore, Lu-Tex/PDT induces apoptosis through selective modulation of members of the Bcl-2 family and differs between BRCE and RPE cells.

L13 ANSWER 8 OF 8 BIOSIS COPYRIGHT (c) 2006 The Thomson Corporation on STN DUPLICATE 2
2000:250893 Document No.: PREV200000250893. **Photodynamic therapy** using Lu-Tex induces apoptosis in vitro and its effect is potentiated by **angiostatin** in retinal capillary endothelial cells. **Renno, R. Z.** [Reprint author]; Delori, F. C.; Holzer, R. A. [Reprint author]; **Gragoudas, E. S.** [Reprint author]; **Miller, J. W.** [Reprint author]. Retina Service, Mass Eye and Ear Inf, Boston, MA, USA. IOVS, (March 15, 2000) Vol. 41, No. 4, pp. S531. print.
Meeting Info.: Annual Meeting of the Association in Vision and Opthalmology. Fort Lauderlade, Florida, USA. April 30-May 05, 2000. Association for Research in Vision and Ophthalmology.
Language: English.

=> s l9 and anti-VEGF
L14 2 L9 AND ANTI-VEGF

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PROCESSING COMPLETED FOR L14
L15 2 DUP REMOVE L14 (0 DUPLICATES REMOVED)

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L15 ANSWER 1 OF 2 SCISEARCH COPYRIGHT (c) 2006 The Thomson Corporation on STN

2003:417665 The Genuine Article (R) Number: 676LY. Anti-vascular endothelial growth factor therapy for subfoveal choroidal neovascularization secondary to age-related macular degeneration - Phase II study results. Fish G; Haller J A; Ho A C; Klein M; Loewenstein J; Martin D; Orth D; Rosen R B; Sanislo S; Schwartz S D; Singerman L J; Williams G; Adamis A P; Blumenkranz M; Goldberg M; **Gragoudas E S**; **Miller J W**; Yannuzzi L; Guyer D R (Reprint); O'Shaughnessy D; Patel S. Eyetech Pharmaceut, 18th Floor, 500 7th Ave, New York, NY 10018 USA (Reprint); Eyetech Pharmaceut, New York, NY 10018 USA. Corporate Author: Eyetech Study Grp. OPHTHALMOLOGY (MAY 2003) Vol. 110, No. 5, pp. 979-986. ISSN: 0161-6420. Publisher: ELSEVIER SCIENCE INC, 360 PARK AVE SOUTH, NEW YORK, NY 10010-1710 USA. Language: English.

ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB Purpose: There is evidence to suggest that anti-vascular endothelial growth factor (**anti-VEGF**) therapy may be useful in treating ocular neovascularization. A phase IA single intravitreal injection study of **anti-VEGF** therapy for patients with subfoveal choroidal neovascularization (CNV) secondary to age-related macular degeneration (AMD) revealed a good safety profile. We performed a phase II multiple injection study of **anti-VEGF** therapy with and without **photodynamic therapy** for patients with subfoveal CNV secondary to AMD to determine the safety profile of multiple injection therapy.

Design: A phase II multiple-dose safety study.

Participants/Methods: Twenty-one patients were treated with intravitreal injection with and without **photodynamic therapy.**

Main Outcome Measures: Clinical evidence of toxicity and complications.

Results: No drug-related serious adverse events were revealed. Ophthalmic evaluation revealed that 87.5% of patients who received the **anti-VEGF** aptamer alone showed stabilized or improved vision 3 months after treatment and that 25% of eyes demonstrated a 3 line or greater improvement in vision on the Early Treatment of Diabetic Retinopathy Study chart during this period. A 60% 3 line gain at 3 months was noted in patients who received both the **anti-VEGF** aptamer and **photodynamic therapy.**

Conclusions: **Anti-VEGF** therapy is a promising treatment for various forms of ocular neovascularization, including AMD. Multiple intravitreal injections of the **anti-VEGF** aptamer were well tolerated in this phase II study. Further clinical trials are necessary to demonstrate the efficacy and long-term safety of **anti-VEGF** therapy for AMD.

L15 ANSWER 2 OF 2 BIOSIS COPYRIGHT (c) 2006 The Thomson Corporation on STN

2003:142492 Document No.: PREV200300142492. Safety and Efficacy of Intravitreal Injection of rhuFab VEGF in Combination With Verteporfin PDT on Experimental Choroidal Neovascularization. Gauthier, D. [Reprint Author]; Husain, D. [Reprint Author]; Kim, I. K. [Reprint Author]; Ezra, E. [Reprint Author]; Tsilimbaris, M. K. [Reprint Author]; Connolly, E. [Reprint Author]; Lane, A. M.; **Gragoudas, E. S.** [Reprint Author]; O'Neill, C. A.; **Miller, J. W.** [Reprint Author]. Retina Service, Angiogenesis Laboratory, Massachusetts Eye and Ear Infirmary, Boston, MA, USA. ARVO Annual Meeting Abstract Search and Program Planner, (2002) Vol. 2002, pp. Abstract No. 566. cd-rom.
Meeting Info.: Annual Meeting of the Association For Research in Vision and Ophthalmology. Fort Lauderdale, Florida, USA. May 05-10, 2002.

Language: English.

AB Purpose: To study the safety and efficacy of intravitreal injection of **anti-VEGF** antibody fragment (rhuFab VEGF) in combination with intravenous verteporfin **photodynamic therapy** (PDT) on experimental choroidal neovascularization in the monkey. Methods: Choroidal neovascularlariation was induced by laser injury in both eyes of cynomolgus monkeys and followed with weekly fundus photography and fluroescein angiography. Two weeks after induction, weekly treatments were started using intravitreal injection of rhuFab VEGF or placebo and PDT. Nine animals received intravitreal injections alternating with PDT. Six of these animals (group I) initially received intravitreal injections and were followed for 63 days. Three of these animals (group II) initially received PDT and were followed for 56 days. Two animals (group III) received injections and PDT the same day at two week intervals and were followed for 56 days. Fluorescein angiograms were graded using a masked, standardized protocol. The data were analyzed using the Stuart-Maxwell chi-square test for matched-pair analysis. Results: Three weeks after the start of treatment, 11 of 11 eyes treated with a combination of rhuFab VEGF injections and PDT showed no leakage from CNV on fluorescein angiography. This finding persisted for 6 weeks of follow-up. In those animals treated with placebo injections and PDT, 7 of 11 eyes showed no leakage from CNV, and 4 showed persistent leakage at 3 weeks. At 6 weeks, 9 of 11 eyes showed no leakage, and 2 eyes showed persistent leakage. Conclusion: Preliminary data indicate that intravitreal rhuFab VEGF in combination with verteporfin PDT causes greater reduction in angiographic leakage than PDT alone in experimental choroidal neovascularization.

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=> s anti-VEGF
L16       2708 ANTI-VEGF

=> s l16 and combination
L17        357 L16 AND COMBINATION

=> s l17 adn PDT
MISSING OPERATOR L17 ADN
The search profile that was entered contains terms or
nested terms that are not separated by a logical operator.

=> s l17 and PDT
L18           3 L17 AND PDT

=> dup remove l18
PROCESSING COMPLETED FOR L18
L19           3 DUP REMOVE L18 (0 DUPLICATES REMOVED)

=> d l19 1-3 cbib abs

L19  ANSWER 1 OF 3  BIOSIS  COPYRIGHT (c) 2006 The Thomson Corporation  on STN
2006:43008  Document No.: PREV200600052209. Expression of vascular endothelial
     growth factor (VEGF) and effects of anti-VEGF
     treatment in the rat chorioretina after photodynamic therapy with
     verteporfin. Li, R. [Reprint Author]; Zhou, S.; Nelkenbrecher, K.; Grant,
     K.; Dhatt, N.; Larkham, S.; Gibbon, K.; Sanghera, J.; Wolin, M.; Margaron,
     P.. IOVS, (2005) Vol. 46, No. Suppl. S, pp. 343.
     Meeting Info.: Annual Meeting of the Association-for-Research-in-Vision-
     and-Ophthalmology. Ft Lauderdale, FL, USA. May 01 -05, 2005. Assoc Res Vis
     & Ophthalmol.
     CODEN: IOVSDA. ISSN: 0146-0404. Language: English.
AB   Purpose: Therapies targeting VEGF are being developed to treat choroidal
     neovascularization (CNV) due to AMD and initial studies have demonstrated
     activity in this disease.  VEGF has been reported to be up-regulated in
     human retina after PDT with verteporfin (Visudyne (R), Novartis
     AG); however, the role that VEGF plays in the posterior segment in
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response to **PDT** is still unknown. Blocking VEGF may prolong CNV closure after **PDT**, but an **anti-VEGF** therapy may also extend the choriocapillaris hypoperfusion noticed after **PDT**, which may lead to potential damage to the retina. We are interested in the **combination** of **PDT** andtherapies targeting VEGF, and specifically, how to optimally and safely applyboth therapies. We investigated the role of VEGF in the biological responses of the chorioretina to **PDT** using an **anti-VEGF** small interfering RNA (siRNA) in the rat eye. Here we report on the expression of VEGF in the chorioretina exposed to **PDT** and the impact of an **anti-VEGF** siRNA on the choriocapillaris after **PDT.** Methods: **PDT** was performed in Long Evans rats using an intravenous bolus injection of 9 mg/m(2) verteporfin followed by 25 J/cm(2) light delivered to the retina at a fluence rate of 150 mW/cm(2). A siRNA that suppressed VEGF expression in rat C6 glioma cells in vitro or, as a control, a siRNA against luciferase was intravitreally injected before or afterPDT. VEGF mRNA extracted from retinas was quantified by real-time RT-PCR. Theexpression of VEGF and VEGF receptors 1 and 2 was also evaluated by immunohistochemistry. Choriocapillaris perfusion was assessed by fluorescein angiography and histology. Results: The choriocapillaris exposed to **PDT** was non-perfusedfor 7-14 days under the tested regimen. Rapid up-regulation of VEGF, VEGFR1 and VEGFR2, and phosphorylation of tyrosine residues on both VEGFRs were detected by immunohistology in the retina 24 h post-**PDT.** An increased level of VEGF mRNA was also confirmed in the **PDT**-treated retinas by real-time RT-PCR. Results of experiments on the effects of siRNA on **PDT**-induced VEGF expression and choriocapillaris closure will be shown. Conclusions: **PDT** induced a temporary choriocapillaris closure which was accompanied by an up-regulation of VEGF and its receptors in the chorioretina. The impact of the **anti-VEGF** siRNA on choriocapillaris hypoperfusion after **PDT** is being evaluated and may provide guidance on the clinical evaluation of the combined use of verteporfin **PDT** with **anti-VEGF** therapies for the treatment of CNV due to AMD.

L19 ANSWER 2 OF 3 MEDLINE on STN

2005452073. PubMed ID: 16118952. [Therapy of the wet form of age-related macular disease: the present state and perspectives]. Terapia wysiekowej postaci zwyrodnienia plamki zwiazanego z wiekiem: stan obecny i perspektywy. Figurska Malgorzata; Stankiewicz Andrzej. (Z Kliniki Okulistyki Wojskowego Instytutu Medycznego w Warszawie.) Klinika oczna, (2005) Vol. 107, No. 4-6, pp. 334-9. Ref: 24. Journal code: 0376614. ISSN: 0023-2157. Pub. country: Poland. Language: Polish.

AB Age-related macular disease (ARMD) is affecting the central part of the retina. ARMD has two major forms: the dry type and the wet type. Although wet type comprises only 15% of ARMD, it is responsible for 90% of severe visual impairment in all ARMD cases. The problem is effective treatment of ARMD, above all its wet type. Laser therapy, retina surgery, TTT and local radiotherapy did not give expected results. The aim of this article is to present modern trends of wet type ARMD therapy, including pharmacotherapy and photodynamic therapy (**PDT**) in relation to pathobiology of choroidal neovascularization (CNV). The goals of pharmacotherapy were discussed in support, that choroidal neovascularization is a dynamic evolution, which includes initiation, active inflammation and non active involution. Cellular mechanisms of photodynamic therapy were presented. It is necessary to accentuate that in the future it can be a **combination** between **PDT** and pharmacotherapy, which inhibits early stage mediators of all types CNV and limits inflammation attendant CNV. These therapeutic approaches ere more likely succeed and included wide spectrum of wet ARMD pathogenesis. The clinical studies show that may be soon we will treat wet form of ARMD using angiostatic steroids, **anti-VEGF** monoclonal antibodies and **anti-VEGF** aptamers.

L19 ANSWER 3 OF 3 BIOSIS COPYRIGHT (c) 2006 The Thomson Corporation on STN
2003:142492 Document No.: PREV200300142492. Safety and Efficacy of Intravitreal Injection of rhuFab VEGF in **Combination** With Verteporfin **PDT** on Experimental Choroidal Neovascularization.
Gauthier, D. [Reprint Author]; Husain, D. [Reprint Author]; Kim, I. K. [Reprint Author]; Ezra, E. [Reprint Author]; Tsilimbaris, M. K. [Reprint Author]; Connolly, E. [Reprint Author]; Lane, A. M.; Gragoudas, E. S. [Reprint Author]; O'Neill, C. A.; Miller, J. W. [Reprint Author]. Retina Service, Angiogenesis Laboratory, Massachusetts Eye and Ear Infirmary, Boston, MA, USA. ARVO Annual Meeting Abstract Search and Program Planner, (2002) Vol. 2002, pp. Abstract No. 566. cd-rom.
Meeting Info.: Annual Meeting of the Association For Research in Vision and Ophthalmology. Fort Lauderdale, Florida, USA. May 05-10, 2002.
Language: English.

AB Purpose: To study the safety and efficacy of intravitreal injection of **anti-VEGF** antibody fragment (rhuFab VEGF) in **combination** with intravenous verteporfin photodynamic therapy (**PDT**) on experimental choroidal neovascularization in the monkey. Methods: Choroidal neovascularization was induced by laser injury in both eyes of cynomolgus monkeys and followed with weekly fundus photography and fluroescein angiography. Two weeks after induction, weekly treatments were started using intravitreal injection of rhuFab VEGF or placebo and **PDT**. Nine animals received intravitreal injections alternating with **PDT**. Six of these animals (group I) initially received intravitreal injections and were followed for 63 days. Three of these animals (group II) initially received **PDT** and were followed for 56 days. Two animals (group III) received injections and **PDT** the same day at two week intervals and were followed for 56 days. Fluorescein angiograms were graded using a masked, standardized protocol. The data were analyzed using the Stuart-Maxwell chi-square test for matched-pair analysis. Results: Three weeks after the start of treatment, 11 of 11 eyes treated with a **combination** of rhuFab VEGF injections and **PDT** showed no leakage from CNV on fluorescein angiography. This finding persisted for 6 weeks of follow-up. In those animals treated with placebo injections and **PDT**, 7 of 11 eyes showed no leakage from CNV, and 4 showed persistent leakage at 3 weeks. At 6 weeks, 9 of 11 eyes showed no leakage, and 2 eyes showed persistent leakage. Conclusion: Preliminary data indicate that intravitreal rhuFab VEGF in **combination** with verteporfin **PDT** causes greater reduction in angiographic leakage than **PDT** alone in experimental choroidal neovascularization.

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=> s angiostatin
L20         4132 ANGIOSTATIN

=> s l20 and PDT
L21           18 L20 AND PDT

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PROCESSING COMPLETED FOR L21
L22           11 DUP REMOVE L21 (7 DUPLICATES REMOVED)

=> d l22 1-11 cbib abs

L22 ANSWER 1 OF 11 EMBASE COPYRIGHT (c) 2006 Elsevier B.V. All rights
    reserved on STN
2005111257 EMBASE Antineovascular therapy, a novel antiangiogenic approach.
    Shimizu K.; Asai T.; Oku N.. Dr. N. Oku, University of Shizouka,
    Department of Medical Biochemistry, School of Pharmaceutical Sciences,
    Shizouka, Japan. oku@u-shizouka-ken.ac.jp. Expert Opinion on Therapeutic
    Targets Vol. 9, No. 1, pp. 63-76 2005.
    Refs: 105.
    ISSN: 1472-8222. CODEN: EOTTAO
    Pub. Country: United Kingdom. Language: English. Summary Language:
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English.
ED Entered STN: 20050324
AB Angiogenesis is a crucial event in tumour growth, since the growth of tumour cells depends on the supply of essentials such as oxygen and nutrients. Therefore, suppression of angiogenesis is expected to show potent therapeutic effects on various cancers. Additionally, this 'antiangiogenic therapy' is thought not only to eradicate primary tumour cells, but also suppress tumour metastases through disruption of haematogenous metastatic pathways. Tumour dormancy therapy does not aim to disrupt newly formed angiogenic vessels but aims to inhibit further formation of neovessels through inhibiting certain processes of angiogenesis. This raises a question of whether or not these antiangiogenic agents bring complete cure of tumours as complete cut-off of oxygen and nutrients is not expected by the treatment with these agents. This paper will review a novel antiangiogenic therapy, antineovascular therapy (ANET). ANET is categorised in antiangiogenic therapy but is different from tumour dormancy therapy using conventional angiogenic inhibitors: ANET aims to disrupt neovessels rather than to inhibit neovessel formation. ANET is based on the fact that angiogenic endothelial cells are growing cells and would be effectively damaged by cytotoxic agents when the agents are effectively delivered to the neovessels. The complete eradication of angiogenic endothelial cells may cause complete cut-off of essential supplies to the tumour cells and lead to indirect but strong cytotoxicity instead of cytostasis caused by the inhibition of angiogenesis. For the purpose of ANET, an angiogenic vasculature-targeting probe has been developed, by which cytotoxic anticancer agents are actively delivered to the angiogenic endothelial cells by using drug delivery system (DDS) technology. Another way to damage newly formed vessels by cytotoxic agents is achieved by metronomic-dosing chemotherapy. This chemotherapy shifts the target of chemotherapeutic agents from tumour cells to angiogenic endothelial cells by selective dosing schedule. Similarly, the shift of target from tumour cells to angiogenic endothelial cells enhanced therapeutic efficacy of cancer photo-dynamic therapy (**PDT**): in this antiangiogenic **PDT**, photosensitizers are delivered more to neovessel endothelial cells than to tumour cells. These therapeutic strategies would be clinically applied in the future. .COPYRGT. 2005 Ashley Publications Ltd.

L22 ANSWER 2 OF 11 EMBASE
2005160028 EMBASE Pharmacological therapy in age-related macular degeneration (AMD). Zou Y.-H.; Chiou G.C.Y.. G.C.Y. Chiou, Dept. of Medical Pharmacol./Toxicol., College of Medicine, Texas A/M System Health Sci. Center, College Station, TX 77843, United States. gchiou@tamu.edu. International Journal of Ophthalmology Vol. 5, No. 1, pp. 8-18 2005.
Refs: 73.
ISSN: 1672-5123. Pub. Country: China. Language: English. Summary Language: English; Chinese.
ED Entered STN: 20050428
AB • Age-related macular degeneration (AMD) is the leading cause of legal blindness in individuals aged over 65 in the United States and other industrialized nations. Till now, we have limited choices of treatment for this kind of disease. Treatment available can be grouped into two major categories: physical and pharmacological therapies. The former received extensive attention with little success whereas the latter attract new attention with great hope of success. The pharmacological therapies include photodynamic therapy (**PDT**), steroids, vascular endothelial growth factor (VEGF) inhibitors, extracellular matrix (ECM) modifiers, gene therapy, nutrition supplements, choroidal blood flow facilitators and the like. **PDT** treatment is the only available effective treatment for certain forms of neovascular AMD. Anecortave acetate, as a synthetic derivative of cortisol, might stabilize vision in patients with predominantly classic subfoveal choroidal neovascularization (CNV) for up to 6mo through subtenon juxtascleral depot application. Intravitreous injection of VEGF aptamer stabilized or improved vision in

87.5% of patients with subfoveal CNV 3mo after treatment. Malfunction of choroidal blood flow is found in early stage of AMD. Elevation of intravascular pressure is the crucial hemodynamic factor in age-related macular degeneration, resulting in a decrease of the blood flow of choriocapillaries. Chain reactions are triggered which lead to retinal pigment epithelium (RPE) degeneration, Bruch's membrane breakdown, CNV formation, AMD and blindness in the end. Therefore, specific drugs that can increase the choroidal blood flow could be very useful to prevent the AMD from developing and worsening. Although most of them are still in the experimental stage, it is hopeful to find a way to treat AMD at the early stage and to prevent the disease to be triggered and developed.

L22 ANSWER 3 OF 11 EMBASE COPYRIGHT (c) 2006 Elsevier B.V. All rights reserved on STN

2005537734 EMBASE Cancer anti-angiogenic therapy. Shimizu K.; Oku N.. N. Oku, Department of Medical Biochemistry, University of Shizuoka, School of Pharmaceutical Sciences, Yada, Shizuoka 422-8526, Japan. oku@u-shizuoka-ken.ac.jp. Biological and Pharmaceutical Bulletin Vol. 27, No. 5, pp. 599-605 2004.
Refs: 113.
ISSN: 0918-6158. CODEN: BPBLEO
Pub. Country: Japan. Language: English. Summary Language: English.

ED Entered STN: 20051215

AB Tumor angiogenesis affords new targets for cancer therapy, since inhibition of angiogenesis suppresses tumor growth by cutting out the supply of oxygen and nutrients. Anti-angiogenic therapy is thought to be free of the severe side effects that are usually seen with cytotoxic anticancer drugs. Furthermore, anti-angiogenic therapy is thought not only to eradicate primary tumor tissues, but also to suppress tumor metastases. However, it is uncertain whether this therapy causes tumor regression because it inhibits only angiogenic events. Recently, a novel anti-angiogenic therapy called anti-neovascular therapy (ANET) has become notable. This therapy inflicts indirect lethal damage on tumor cells by damaging newly formed blood vessels using anti-cancer drugs targeting the angiogenic vasculature, since cytotoxic anti-cancer drugs cause damage to proliferating neovascular endothelial cells as well as tumor cells. Moreover, neovascular endothelial cells would not be expected to acquire drug-resistance. Traditional chemotherapy, which directly targets tumor cells, has potential problems such as low specificity and severe side effects. On the contrary, in ANET, severe side effects may be suppressed, since traditional anti-cancer agents are delivered to the neovessels by DDS technology. Besides the usage of DDS technology, anti-neovascular scheduling of chemotherapy, or metronomic-dosing chemotherapy, has also been attempted in which anti-cancer drugs are administered on a schedule to damage neovessels. In this review, we describe traditional anti-angiogenic therapy and ANET. We also discuss anti-angiogenic cancer photodynamic therapy (**PDT**), since **PDT** is clinically applied to treat age-related macular degeneration (AMD), in which uncontrolled angiogenesis occurs. .COPYRGT. 2004 Pharmaceutical Society of Japan.

L22 ANSWER 4 OF 11 SCISEARCH COPYRIGHT (c) 2006 The Thomson Corporation on STN

2003:1054374 The Genuine Article (R) Number: 709CH. Enhanced photodynamic therapy using **angiostatin** with verteporfin **PDT** in a laser-injury rat model. Terada Y (Reprint); Michaud N A; Connolly E J; Lane A; Ohtsuki H; Gragoudas E S; Miller J W. Massachusetts Eye & Ear Infirm, Retina Serv, Angiogenesis & Laser Lab, Boston, MA 02114 USA; Okayama Univ, Sch Med, Okayama 700, Japan. INVESTIGATIVE OPHTHALMOLOGY & VISUAL SCIENCE (MAY 2003) Vol. 44, Supp. [1], pp. U408-U408. MA 1749.
ISSN: 0146-0404. Publisher: ASSOC RESEARCH VISION OPHTHALMOLOGY INC, 12300 TWINBROOK PARKWAY, ROCKVILLE, MD 20852-1606 USA. Language: English.

L22 ANSWER 5 OF 11 EMBASE COPYRIGHT (c) 2006 Elsevier B.V. All rights reserved on STN

2003249645 EMBASE Photodynamic therapy for choroidal neovascularization. The Jules Gonin Lecture, Montreux, Switzerland, 1 September 2002. Miller J.W.. J.W. Miller, Angiogenesis and Laser Laboratories, Harvard Medical School, Massachusetts Eye and Ear Infirmary, Boston, MA, United States. jwmiller@meei.harvard.edu. Graefe's Archive for Clinical and Experimental Ophthalmology Vol. 241, No. 4, pp. 258-262 1 Apr 2003.
Refs: 30.
ISSN: 0721-832X. CODEN: GACODL
Pub. Country: Germany. Language: English.
ED Entered STN: 20030710
AB In summary, the targeted verteporfin and verteporfin-PVA were both more efficient at CNV closure than unbound verteporfin. VEGFR2-targeted verteporfin appeared to be selective when normal retina and choroid were treated, resulting in choriocapillaris closure with minimal effect on RPE or neurosensory retina. In contrast, the verteporfin-PVA control showed non-selective retinal damage. These positive findings will be pursued further in experimental models and will hopefully warrant clinical investigation in the future. Another direction that we also wish to pursue would be to modulate the **PDT** response in normal and diseased tissue using factors in the apoptosis pathway, and preliminary in vitro work supports this strategy [27]. We would also like to improve drug delivery for anti-angiogenic and neuroprotective agents and towards this end have been working on a trans-scleral drug delivery approach.

L22 ANSWER 6 OF 11 BIOSIS COPYRIGHT (c) 2006 The Thomson Corporation on STN
2003:529243 Document No.: PREV200300524981. ENHANCED PHOTODYNAMIC THERAPY USING **ANGIOSTATIN** WITH VERTEPORFIN **PDT** IN A LASER - INJURY RAT MODEL. Terada, Y. [Reprint Author]; Michaud, N. A. [Reprint Author]; Connolly, E. J. [Reprint Author]; Lane, A. [Reprint Author]; Ohtsuki, H.; Gragoudas, E. S. [Reprint Author]; Miller, J. W. [Reprint Author]. Retina Service, Angiogenesis and Laser Laboratory, Mass Eye and Ear Infirmary, Boston, MA, USA. ARVO Annual Meeting Abstract Search and Program Planner, (2003) Vol. 2003, pp. Abstract No. 1749. cd-rom.
Meeting Info.: Annual Meeting of the Association for Research in Vision and Ophthalmology. Fort Lauderdale, FL, USA. May 04-08, 2003. Association for Research in Vision and Ophthalmology.
Language: English.
AB Purpose: Previous studies had shown increased cytotoxicity of verteporfin photodynamic therapy (**PDT**) combined with the anti-angiogenic drug **angiostatin** for bovine retinal microcapillary endothelium (bRME) but not for human retinal pigment epithelium (hRPE) in vitro. Here, we investigated the selectivity and the efficacy of **PDT** combined with **angiostatin** in vivo. Methods: Choroidal neovascular membranes (CNV) were induced in Brown-Norway rats using Argon/Dye laser. After the initial laser CNV induction, rats were treated with either **angiostatin** bolus injections intraperitoneally (12 and 24 hours before **PDT**) at 50 mg/kg or continuous administration of **angiostatin** through subcutaneously implanted osmotic pumps at 15mg/kg/day. Verteporfin **PDT** was performed at verteporfin dose of 3 or 6 mg/m2 using an irradiance of 600mW/cm2 and fluence of 10 and 25 J/cm2. Fluorescein angiograms performed 20 days after laser injury but before **PDT**, as well as 1 and 7 days after **PDT** were graded in a masked fashion using grading standards of CNV leakage. Non-parametric and parametric techniques were used to evaluate treatment effects. Results: **Angiostatin** alone did not prevent CNV growth using either model of administration. Bolus intraperitoneal administration of **angiostatin** prior to verteporfin **PDT** did not increase the efficacy of verteporfin **PDT** on CNV closure (P>.40 for differences in leakage between eyes treated with **PDT** vs. **PDT** with **angiostatin** at both timepoints and fluences).Continuous subcutaneous administration of **angiostatin** was significantly associated with CNV closure (beta=2.63, P=.002) in regression analysis adjusting for the effects of fluence. Conclusions: Continuous administration of **angiostatin** potentiated the efficacy of verteporfin **PDT** for CNV closure in a laser-injury

rat model. Combined therapy of anti-angiogenic drugs and **PDT** may limit the damage to normal structure and improve **PDT** results.

L22 ANSWER 7 OF 11 MEDLINE on STN DUPLICATE 1
2002649629. PubMed ID: 12408983. Release of regulators of angiogenesis following Hypocrellin-A and -B photodynamic therapy of human brain tumor cells. Deininger Martin H; Weinschenk Toni; Morgalla Matthias H; Meyermann Richard; Schluesener Hermann J. (Institute of Brain Research, University of Tubingen, Calwer Strasse 3, D-72076 Tubingen, Germany.. martin.deininger@uni-tuebingen.de) . Biochemical and biophysical research communications, (2002 Nov 8) Vol. 298, No. 4, pp. 520-30. Ref: 83. Journal code: 0372516. ISSN: 0006-291X. Pub. country: United States. Language: English.

AB Photodynamic therapy (**PDT**) is an innovative strategy for the treatment of solid neoplasms of the brain. Aside from inducing cell death in tumor cells, **PDT** induces endothelial cell death and promotes formation of blood clots; however, exact mechanisms that trigger these phenomena remain largely unknown. We now used Western blotting to analyze secretion of regulators of angiogenesis to the supernatants of one glioma, one macrophage, and one endothelial cell line following Hypocrellin-A and -B photodynamic therapy. We observed induction of proangiogenic VEGF (vascular endothelial growth factor) and of antiangiogenic sFlt-1, **angiostatin**, p43, allograft inflammatory factor-1, and connective tissue growth factor. Release of thrombospondin-1 was diminished in a glioma cell line supernatant. Endostatin release was induced in glioma cells and reduced in macrophages and endothelial cells. These data show that a wide range of antiangiogenic factors are secreted by brain tumor cells following Hypocrellin photochemotherapy. However, VEGF release is also induced thus suggesting both favorable and deleterious effects on tumor outgrowth.

L22 ANSWER 8 OF 11 SCISEARCH COPYRIGHT (c) 2006 The Thomson Corporation on STN
2003:955111 The Genuine Article (R) Number: 709CF. Modified verteporfin photodynamic therapy (**PDT**), **PDT** combined with **angiostatin** in vitro and in vivo. Terada Y (Reprint); Zacks D N; Connolly E J; Michaud N; Gragoudas E S; Miller J W. Harvard Univ, Sch Med, Massachusetts Eye & Ear Infirm, Retina Serv, Angiogenesis & Laser Res Lab, Boston, MA USA. INVESTIGATIVE OPHTHALMOLOGY & VISUAL SCIENCE (MAY 2002) Vol. 43, Supp. [1], pp. U114-U114. MA 574. ISSN: 0146-0404. Publisher: ASSOC RESEARCH VISION OPHTHALMOLOGY INC, 12300 TWINBROOK PARKWAY, ROCKVILLE, MD 20852-1606 USA. Language: English.

L22 ANSWER 9 OF 11 BIOSIS COPYRIGHT (c) 2006 The Thomson Corporation on STN
2003:142500 Document No.: PREV200300142500. Modified Verteporfin Photodynamic Therapy (**PDT**), **PDT** Combined With **Angiostatin** In Vitro and In Vivo. Terada, Y. [Reprint Author]; Zacks, D. N. [Reprint Author]; Connolly, E. J. [Reprint Author]; Michaud, N. [Reprint Author]; Gragoudas, E. S. [Reprint Author]; Miller, J. W. [Reprint Author]. Angiogenesis and Laser Research Laboratory, Retina Service, Mass Eye and Ear Infirmary, Harvard Medical School, Boston, MA, USA. ARVO Annual Meeting Abstract Search and Program Planner, (2002) Vol. 2002, pp. Abstract No. 574. cd-rom.
Meeting Info.: Annual Meeting of the Association For Research in Vision and Ophthalmology. Fort Lauderdale, Florida, USA. May 05-10, 2002.
Language: English.

AB Purpose: To investigate the selectivity and the efficacy of **PDT** combined with the anti-angiogenic drug **angiostatin** in vitro and in vivo. Methods: (in vitro) Human retinal pigment epithelial (hRPE) and bovine retinal microvascular endothelial cells (bRME) were maintained in conditioned media. Verteporfin **PDT** was performed on cells with or without prior exposure to 100ng/mL of **angiostatin.** Cellular survival was assessed at 24 hours after **PDT.** (in vivo) Choroidal neovascular membranes (CNV) were induced in Brown-Norway rats using

Argon/Dye laser. Four groups were studied: 1. control rats (placebo), 2. **angiostatin** alone (50mg/kg) 1 and 2 weeks after CNV induction, 3. verteporfin **PDT** alone and 4. **PDT** plus 50mg/kg of **angiostatin** 12 and 24 hours prior to **PDT** at verteporfin dose of 3mg/m2 using an irradiance of 600mW/cm2 and fluence of 10 and 25 J/cm2. Fluorescein angiography was performed at 3 and 4 weeks after CNV induction and at 24 hours and 7 days after **PDT**, and graded in a masked standardized fashion. Results: In vitro results showed increased cytotoxicity for bRME but for hRPE when **angiostatin** was combined with verteporfn **PDT**. In vivo results showed that **angiostatin** alone did not prevent CNV, and there was no increased efficacy when **angiostatin** was administered prior to verteporfin **PDT** at the doses tested. Conclusion: **Angiostatin** potentiated the efficacy of verteporfin **PDT** for microvascular endothelium. However, in vivo **angiostatin** did not appear to potentiate the effect of verteporfin **PDT** on CNV at the doses tested.

L22 ANSWER 10 OF 11 CAPLUS COPYRIGHT 2006 ACS on STN
2001:597738 Document No. 135:149263 Methods and compositions for treating condition of the eye. Miller, Joan W.; Gragoudas, Evangelos S.; Renno, Reem Z. (Massachusetts Eye and Ear Infirmary, USA). PCT Int. Appl. WO 2001058240 A2 20010816, 46 pp. DESIGNATED STATES: W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, US, UG, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG, TR. (English). CODEN: PIXXD2. APPLICATION: WO 2001-US4231 20010209. PRIORITY: US 2000-PV181641 20000210.

AB Provided are methods and compns. for the photodynamic therapy (**PDT**) of ocular conditions characterized by the presence of unwanted choroidal neovasculature, for example, neovascular age-related macular degeneration. The selectivity and sensitivity of the **PDT** method can be enhanced by combining the **PDT** with an anti-angiogenesis factor, for example, **angiostatin** or endostatin, or with an apoptosis-modulating factor. Furthermore, the selectivity and sensitivity of the **PDT** may be further enhanced by coupling a targeting moiety to the photosensitizer so as to target the photosensitizer to choroidal neovasculature.

L22 ANSWER 11 OF 11 MEDLINE on STN DUPLICATE 2
2001025053. PubMed ID: 11053300. Photodynamic therapy using Lu-Tex induces apoptosis in vitro, and its effect is potentiated by **angiostatin** in retinal capillary endothelial cells. Renno R Z; Delori F C; Holzer R A; Gragoudas E S; Miller J W. (Laser Laboratory, Retina Service, Massachusetts Eye and Ear Infirmary. Schepens Eye Research Institute, Harvard Medical School, Boston, USA.) Investigative ophthalmology & visual science, (2000 Nov) Vol. 41, No. 12, pp. 3963-71. Journal code: 7703701. ISSN: 0146-0404. Pub. country: United States. Language: English.

AB PURPOSE: To examine the effect of combining **angiostatin** with photodynamic therapy (**PDT**) using Lutetium Texaphyrin (Lu-Tex; Alcon, Fort Worth, TX) as a photosensitizer in bovine retinal capillary endothelial (BRCE) and retinal pigment epithelial (RPE) cells and to determine the mode of **PDT**-induced cell death in these cell lines. METHODS: Cultured BRCE and RPE cells were incubated with **angiostatin** (500 ng/ml) for 18 hours and subjected to Lu-Tex/ **PDT**, using treatment parameters previously optimized (3 microgram/ml Lu-Tex for 30 minutes followed by timed irradiation at 732 nm). Cellular survival was assessed after a 1-week cellular proliferation. Data were analyzed using Student's t-test. Caspase 3 activity was monitored in cells after **PDT** using a fluorogenic substrate, (Asp-Glu-Val-Asp)-AFC (7-amino-4-trifluoromethyl coumarin)

[DEVD-AFC], of caspase 3. After **PDT**, expression of Bcl-2, Bcl-x(L), Bax, and Bak was also examined in cell lysates by Western blot analysis. RESULTS: A synergistic cytotoxic effect of **angiostatin** and Lu-Tex/**PDT** was observed in BRCE cells at all fluences used (5, 10, and 20 J/cm(2); P </= 0.05). These findings applied only if **angiostatin** was delivered before **PDT**. No such interactive killing effect was observed in RPE cells. Caspase 3 activity was elevated within 10 minutes of **PDT** in BRCE and RPE cells and was fluence dependent. Differential modulation of Bcl-2 family members was observed after **PDT** in BRCE and RPE cells. CONCLUSIONS: The combination of **angiostatin** and Lu-Tex/**PDT** potentiates the cytotoxic effect of Lu-Tex/**PDT** on BRCE but not on RPE cells. This may provide a strategy to increase the selectivity of **PDT** in damaging capillary endothelial cells with less damage to RPE cells. Lu-Tex/**PDT** induces rapid caspase-dependent apoptosis in BRCE and RPE cells. Furthermore, Lu-Tex/**PDT** induces apoptosis through selective modulation of members of the Bcl-2 family and differs between BRCE and RPE cells.

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